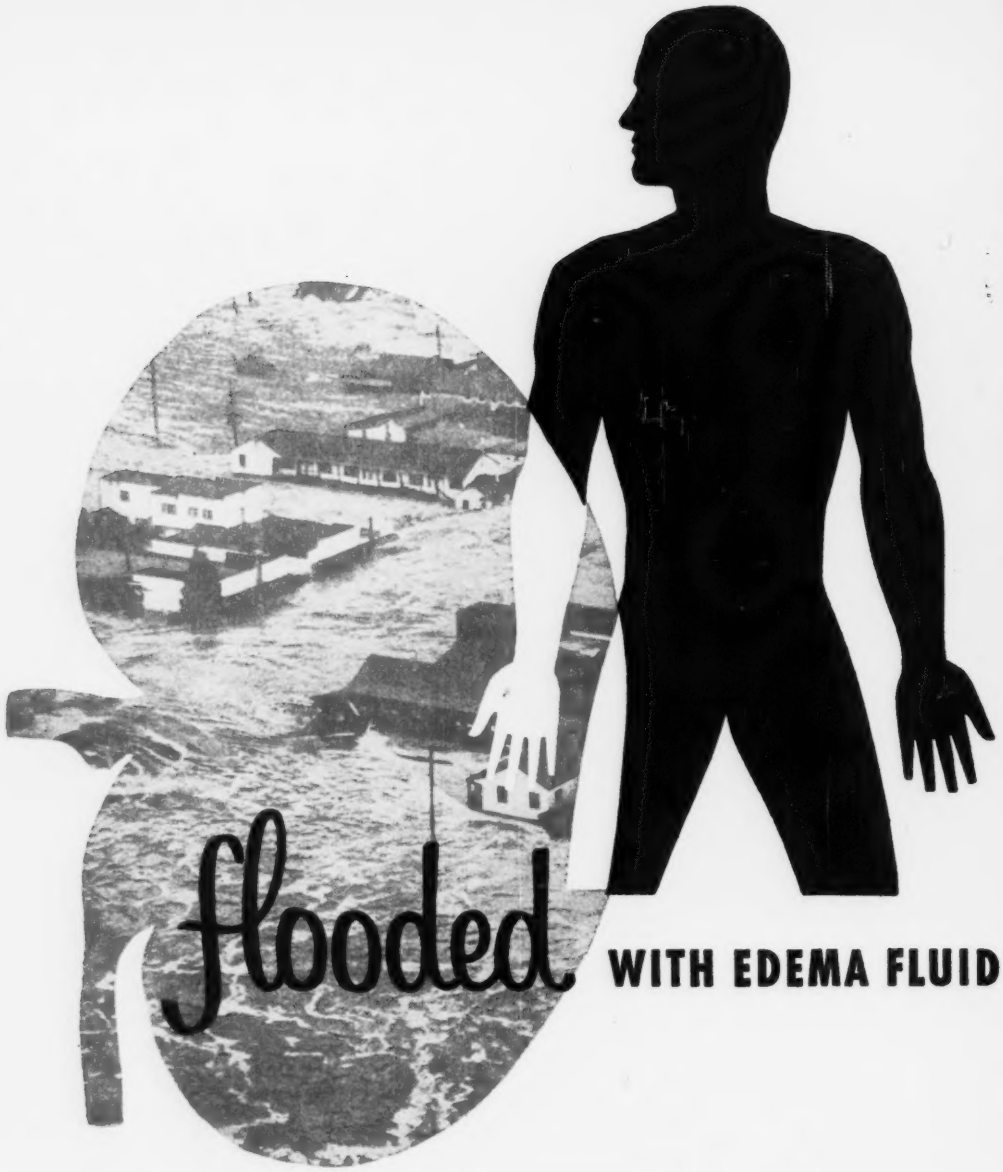
JULY 1957
VOL. XVI NO. 1

Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

30th Scientific Sessions of the American Heart Association
Commemorating the Tercentenary of William Harvey
Chicago, Ill., from October 25–28, 1957

Published by Grune & Stratton, Inc.



WITH EDEMA FLUID

SALYRGAN®-THEOPHYLLINE

drains off edema fluid in nephrosis, hepatic cirrhosis and congestive failure. By eliminating massive amounts of fluid, Salyrgan-Theophylline reduces the load placed upon the heart and increases cardiac efficiency.

Winthrop LABORATORIES
NEW YORK 18, N. Y.

Ampuls of 1 cc. and 2 cc. Enteric coated tablets.

Salyrgan (brand of mersalyl), trademark reg. U.S. Pat. Off.

Circulation

JULY, 1957
VOL. XVI NO. 1

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

Heart Disease as a Cause of Death

THE statement is frequently seen, not only in scientific literature but also in the lay press, that heart disease is increasing as a cause of death, and this tendency is frequently contrasted with the death rate from tuberculosis, which is reported as rapidly decreasing. This editorial is designed to draw attention to a difference between these 2 situations that is of importance in any consideration of this subject.

There is no doubt concerning the facts. In recent years, doctors practicing in the United States have been writing heart disease as the cause of death on the death certificates of their patients with increasing frequency; similarly, they have been writing tuberculosis as a cause of death with diminishing frequency. The statisticians, with knowledge gained by studying the death certificates forwarded to departments of public health by these doctors, have amply demonstrated that the 2 tendencies, of the one to increase and of the other to decrease, cannot logically be attributed to chance. These are the facts.

Needless to say, the statisticians analyzing the data are altogether dependent on what thousands of doctors write on the death certificates, and so their conclusions that tuberculosis is decreasing and that heart disease is increasing in the population are not facts, but inferences. It is these inferences I wish to examine. Let us do so by asking 2 questions: under what conditions do doctors write tuberculosis on death certificates as a cause of death; under what conditions do they write heart disease as a cause of death?

To the first of these questions, I find the answer easy and satisfying. Tuberculosis is a long continuing febrile disease readily diagnosed by objective tests, the demonstration of tubercle bacilli, the characteristic x-ray appearance, and the characteristic lesions found at necropsy. While I doubt if enough of the cases have been subjected to necropsy to influence the statistics, tuberculosis is diagnosed so easily, and with so much certainty, that I have little doubt that when doctors attribute death to tuberculosis they are right about it in the great majority of instances. I heartily concur in the belief that deaths from tuberculosis are decreasing.

But an answer to the question, what is implied when doctors write heart disease on the death certificate, is not so easily given. Several things seem evident: such clear entities as rheumatic, thyroid, and syphilitic heart disease are not being diagnosed more frequently as causes of death; the type of heart disease being diagnosed more frequently is that found in patients in the latter half of life, and these deaths are attributed to arteriosclerotic or coronary heart disease.

Doubtless, in many instances such a diagnosis is well based. Certainly, most doctors would attribute death to heart disease if the patient had suffered from angina pectoris or cardiac infarction, and no other cause of death was obvious, if he had died in congestive failure, or if he dropped dead without obvious cause. But I am sure that at the present time this diagnosis is not being limited to patients with such histories.

If arteriosclerotic disease of the coronary arteries was found at necropsy, one would be justified as reporting it as cause of death, if no other cause was obvious. Yet it is evident that this situation is not as clear as was once thought. If the patient has had angina or cardiac infarction, the chances of coronary arteriosclerosis being found at necropsy are very

high, and this has long been emphasized. But the medical profession as a whole has been slow in realizing that in many cases, coronary arteriosclerosis has been found at necropsy in persons who never had angina or infarction, and who died from a remote cause. My old friend Dr. W. O. Abbott, whose untimely death was a great loss to American medicine, used to suggest that the design of the clinicopathologic conference should be reversed: the pathologist should perform the autopsy in complete ignorance of the case history and physical findings and from his autopsy findings he should attempt to reconstruct the history and physical findings. I believe, myself, that such blind tests are badly needed and that such a conference would be a very healthy and informing teaching exercise.

But, in all probability, of the cases reported as dying from heart disease, not enough have been subjected to necropsy to seriously affect the statistics that are the subject of this editorial; to my mind, the real difficulty lies elsewhere. This difficulty stems from the fact that the identification of the heart as cause of death presents a problem different from that of any other organ of the body.

It is when the heart stops beating that the patient is pronounced dead, and this fact makes for confusion of thought and overemphasizes the relation between death and the heart. All the organs fail at death; this is a truism of no importance and we do not even enter the fact in our records. It is the primary cause of death that properly concerns us, and we seek to identify and record the factor or factors that initiated the train of events leading to the death of all organs. But the heart's failure at death is so much more conspicuous than is the failure of the other organs, that one is always tempted to think of the heart's failure as the cause of the failure of the other organs. Let us consider a concrete situation as an example of what I mean. An elderly patient is suffering from an electrolyte imbalance and his attending physician, practicing his calling without the opportunity for elaborate studies, observes the weakening pulse and the falling blood pressure as life ebbs away. Certainly nothing easily perceived by his senses points to the adrenal or to the kidney as the primary source of difficulty, while he has abundant evidence of the weakening heart. Surely that doctor would write heart disease on the death certificate, and if the patient was elderly he would write arteriosclerotic heart disease. It is true that in a sense the doctor would be right, for it was when the heart stopped that the patient was pronounced dead. Yet the writing of heart disease on the death certificate in such situations is worse than meaningless, it confuses those attempting to draw conclusions from the data.

It is my contention that a confusion of this kind happens very frequently in the practice of medicine, for doctors must write some cause of death on the death certificate. When no other cause of death is readily apparent, the cessation of the heart's action will be attributed to trouble primarily in the heart itself, especially if the patient is elderly. So it is my strong impression that arteriosclerotic heart disease is being written on the death certificates of most elderly persons whose primary cause of death is either unknown or unclear to the attending physician; and that doctors often diagnose heart disease in elderly people, not for positive reasons, as is the case with the diagnosis of tuberculosis, but for negative reasons: they do not know what else to call it.

Therefore, I believe that, as knowledge of primary causes of disease increases, and as studies that disclose such causes become more widely available, the group in which death is now being attributed to arteriosclerotic heart disease will be found to be extremely diverse. The fact that the relative frequency with which death is attributed to arteriosclerotic heart disease varies so in different parts of the nation is difficult to explain and the finding excites my suspicion that the data are being contaminated in the fashion I have suggested; diagnostic fashions change with time as well as with place. For these reasons the reported increase in the number of deaths from arteriosclerotic heart disease seems to me difficult to interpret with confidence. The concept that tuberculosis is decreasing as a cause of death seems far more firmly based.

ISAAC STARR

Tricuspid Stenosis

Physiologic Criteria for Diagnosis and Hemodynamic Abnormalities

By THOMAS KILLIP III, M.D., AND DANIEL S. LUKAS, M.D.

Physiologic criteria for the diagnosis of tricuspid stenosis have not been satisfactorily established. In an attempt to define these criteria the pressure gradients across the tricuspid valve during right ventricular diastole were analyzed in 10 patients with tricuspid stenosis and compared with the gradients in a group of patients who did not have this lesion. The diagnostic importance of the mean gradient is emphasized. The hemodynamic abnormalities associated with the tricuspid stenosis are presented and discussed.

LESIONS of the tricuspid valve are frequently unrecognized until they are associated with advanced signs and symptoms. The problems involved in the diagnosis of tricuspid insufficiency have recently been emphasized.[1, 2] Similar difficulty prevails with regard to tricuspid stenosis. Information about the clinical and physiologic spectrum that can be produced by this disease is scant. Since surgical therapy is indicated in selected cases, the need for precision in diagnosis and evaluation of the functional severity of this lesion is apparent.

The present paper contains the data on 10 patients with tricuspid stenosis and emphasizes the hemodynamic criteria necessary for diagnosis and the physiologic alterations produced by this deformity. The clinical aspects of these patients are discussed in a separate communication.[3]

MATERIALS AND METHODS

In 9 of the 10 patients the diagnosis of tricuspid stenosis was suspected clinically, in the other it was made from the hemodynamic data and confirmed at autopsy. Of the 5 patients who were in normal sinus rhythm, the lesion was isolated in FC, combined with mitral stenosis in ER, RP, and JP, and combined with mitral and aortic stenosis in EH. All 5 of the patients with atrial fibrillation had associated tricuspid insufficiency and mitral stenosis and insufficiency. Of this group, SG and LR did not have aortic valvular disease; RR and JF had a double aortic lesion, and AN had aortic stenosis. JP was 14 weeks pregnant at the time of study. All 10 patients were female. Their ages ranged from 23 to 52 and averaged 37 years. Following diagnostic studies JP and RP underwent mitral valvuloplasty; SG had a mitral and a tricuspid valvuloplasty, and FC underwent a tricuspid valvuloplasty.

Cardiac catheterization was performed on all patients (table 1). It was repeated 13 months after tricuspid valvuloplasty in FC, following a 29-month interval in JF and after 39 months in RR. The technic of catheterization and the accessory analytic methods employed were as previously described.[4, 5] Pressures were measured with a Sanborn electromanometer and recorded by a 4-channel Polyviso recorder. In recording right atrial and ventricular diastolic pressures a sensitivity of 40 mm. Hg per 4-cm. deflection was utilized, since it provides records that are easily and accurately read and yet are free of the artifacts frequently recorded at higher sensitivities. Right ventricular and atrial pressures were determined in succession through a single-lumen catheter except in patient LR, in whom they were recorded simultaneously through a double-lumen catheter.

The mean pressures in right atrium and right ventricle during ventricular diastole and the gradient during flow across the tricuspid valve were determined by graphic integration—points read on the pressure curves for every 0.04 second of ventricular diastole were averaged. Sufficient cardiac cycles were analyzed to include an entire respiratory cycle. The peak of the R-wave in lead II of the simultaneously recorded electrocardiogram was used as a reference point to plot the beginning and end of ventricular diastole on the atrial curve. The ventricular pressure at right ventricular end-diastole (RVed) and the corresponding pressure point on the right atrial curve (so-called Z-point) were also analyzed.

The areas of the tricuspid and mitral valve orifices were calculated from the formula of Gorlin and Gorlin,[6] with the recommended correction factors. The diastolic filling period was determined from the

From the Cardio-Pulmonary Laboratory and the Department of Medicine of the New York Hospital-Cornell Medical Center, New York, N. Y.

This study was supported by grant H-1810 (C) from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service.

Presented in part at the National Meeting of the American Federation for Clinical Research, Subsection on Cardiovascular Disease, Atlantic City, April 29, 1956.

TABLE 1.—*Data Obtained at Cardiac Catheterization in Ten Patients with Triscupid Stenosis*

Patient		O_2 Consumption ml./min./M.²	Cardiac index L./min./M.²	Cardiac rate	Pressures in mm. Hg			Pulmonary vascular resistance (dynes-sec.-cm.$^{-5}$)	Mitral valve area (cm.²)
					Right atrial mean	Pulmonary artery systolic/diastolic mean	Pulmonary "capillary" mean		
F. C.	R	111	1.91	88	6	15/5, 10	5	140	—
	E	214	2.07	126	11	23/12, 15	10	130	—
F. C.*	R	112	1.72	90	7	17/8, 13	10	95	—
	E	267	2.71	140	13	26/17, 22	17	100	—
E. R.	R	145	1.52	84	8	24/9, 14	10	136	1.1
	E	294	1.90	112	17	32/16, 26	21	136	0.9
R. P.	R	103	2.48	68	5	24/9, 14	11	57	1.2
	E	231	2.53	88	7	35/20, 28	24	74	1.0
J. P.	R	121	3.06	90	6	29/15, 21	16	86	1.2
	E	263	3.41	100	12	42/26, 33	17	92	1.1
E. H.	R	174	2.99	80	8	25/10, 20	14	97	1.6
	E	243	3.73	100	10	39/14, 26	17	146	1.9
S. G.	R	195	1.69	110	21	45/27, 37	27	292	0.8
	E	—	—	110	29	50/31, 42	32	—	—
R. R.	R	114	2.28	76	14	48/22, 30	23	165	1.0
R. R.*	R	120	2.36	85	18	44/—, —	—	—	—
A. N.	R	133	1.74	100	21	55/36, 45	—	—	—
L. R.	R	144	3.12	70	12	45/18, 27	12	263	1.6
	E	—	—	90	19	67/—, —	—	—	—
J. F.	R	138	1.76	92	9	57/28, 38	28	310	0.5
J. F.*	R	143	1.71	90	15	123/55, 71	22	1809	0.6

* Second Study R: Rest E: Exercise

right ventricular pressure tracing. For calculation of the tricuspid orifice area this interval was measured from the point during isometric relaxation at which right atrial and ventricular pressures were equal to the point during isometric contraction at which they again equalized (figs. 3 and 5).

Control Data

To determine the range in diastolic atrioventricular gradient that may be encountered in applying the present method to nonstenotic tricuspid valves, the catheterization data at rest of 14 patients with rheumatic heart disease who eventually came to autopsy and were demonstrated *not* to have tricuspid stenosis were reviewed. All had mitral stenosis and many had additional valvular lesions, including severe tricuspid insufficiency. Nine patients had atrial fibrillation, 5 normal sinus rhythm. The mean right atrioventricular diastolic gradient at rest was −0.1 mm. Hg (S.D. ± 1.0) with a range of −2.1 to +1.4 (fig. 1).

Since satisfactory studies during exercise were available on only 4 of the autopsied patients, atrioventricular gradients during exercise from an additional 7 patients with rheumatic heart disease who did not have any clinical stigmata of tricuspid stenosis[3] were also determined. In the combined series of 11 patients the mean gradient was +0.5 mm. Hg (S.D. ± 1.1), with a range of −1.6 to +2.2 (fig. 1).

In the patients studied at rest the mean Z-RVed gradient was −1.0 (S.D. ± 1.1) mm. Hg, with a range of −3.8 to +2.4. During exercise the mean Z-RVed gradient was −2.3 mm. Hg (S.D. ± 1.9), with a range of −4.8 to +1.0.

RESULTS

Atrioventricular Gradient

At rest the mean right atrial pressure during ventricular diastole significantly exceeded the mean right ventricular diastolic pressure in all 10 patients with tricuspid stenosis (table 2). In general, the gradients were small, ranging from 2.9 to 11.9 mm. Hg (fig. 1). In 9 of the 10 patients it was less than 7 mm. Hg; in 4 it was less than 5 mm. Even the smallest gradients, however, were readily appreciated by gross inspection of the curves* when the pressures in the right atrium and ventricle were recorded at

* When records for the control series were reviewed a previously unrecognized gradient in the tracings of JF was visually apparent. Examination of the postmortem specimen revealed a moderately severe stenosis of the tricuspid valve. This experience added considerable confidence in the validity of the present methods.

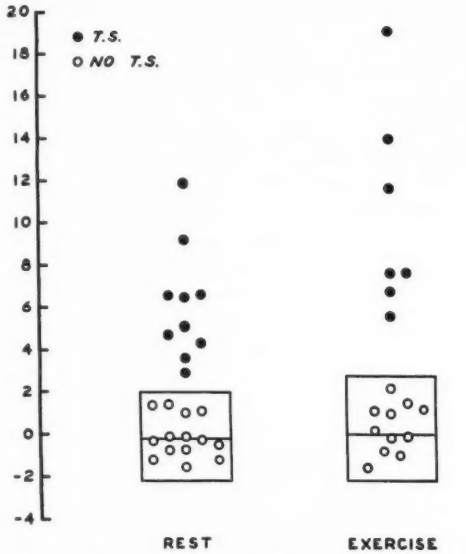


FIG. 1. Mean pressure gradients (*ordinate*, mm. Hg) across tricuspid valve during right ventricular diastole at rest and during exercise in patients with tricuspid stenosis and a group of patients with rheumatic heart disease without tricuspid stenosis. Rectangles enclose data from group without stenosis; horizontal lines represent means.

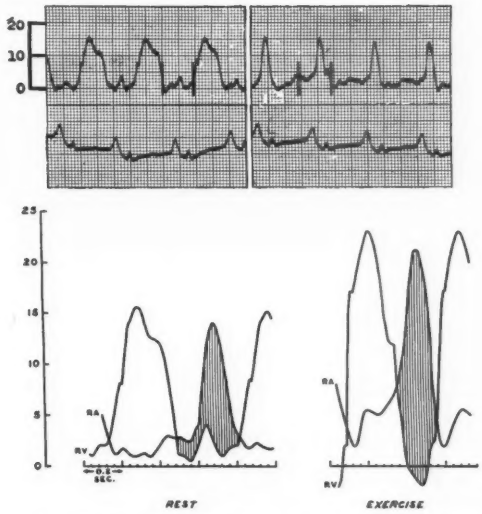


FIG. 2. *Top.* Right ventricular and atrial pressure tracings at rest from patient (FC) with isolated tricuspid stenosis and normal sinus rhythm. Functional diastole set-off between vertical lines. Note amplitude of atrial contraction and obvious gradient during diastole. Calibration at left, as in all subsequent pressure curves, in mm. Hg.

FIG. 3 *Bottom.* Right atrial and ventricular pressure curves from FC (fig. 2) at rest and during exercise redrawn and superimposed. Vertical linear shading defines gradient. Note gradient is maximal during late diastole when atrium contracts and increases during exercise.

the same sensitivity (fig. 2). The largest gradients at rest were noted in the patients with atrial fibrillation, all of whom had associated tricuspid insufficiency.

The manner in which the gradient varied during the course of ventricular diastole depended on the rhythm. In normal sinus rhythm it was usually small early in diastole, but became considerable during atrial contraction, which produced a pressure wave of exceptionally large amplitude (figs. 2 and 3). In atrial fibrillation a constant level of right atrial pressure during diastole and an early diastolic dip in right ventricular pressure gave rise to a gradient that was largest early in diastole (figs. 4 and 5).

During exercise the gradient increased in every patient in whom adequate studies were available (table 2, fig. 6). The increase resulted from a rise in mean atrial pressure, an augmented amplitude of atrial contraction when present, and an accentuated dip in right ventricular pressure early in diastole.

Respiration often produced striking effects on the mean diastolic gradient, which was maximal during inspiration and minimal during expiration (fig. 7). In general, right atrial pressure varied little with the phases of respiration, whereas right ventricular diastolic pressure fell with inspiration and rose with expiration.

Right atrial pressure at the Z-point was higher than the RVed pressure in all patients, but did not provide an index of the level of the mean diastolic gradient. Indeed in 4 patients, including FC, who required subsequent tricuspid valvuloplasty, this difference was no greater than in the control series. Exercise increased the Z-RVed difference in all but 1 patient. This marked disparity in pressures at the onset of right ventricular contraction was especially striking in those with normal sinus rhythm and was caused by the onset of ven-

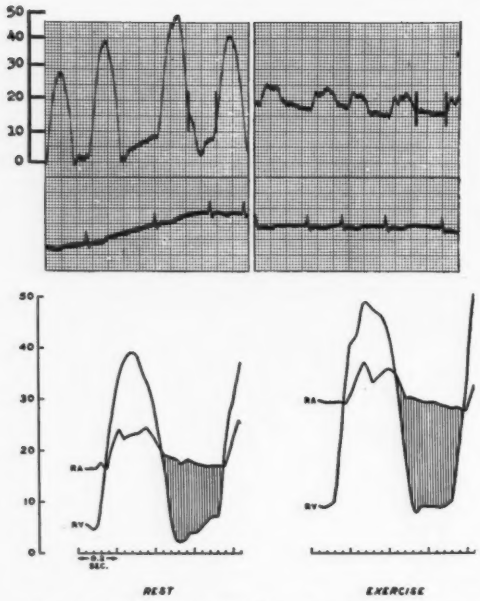


FIG. 4. *Top.* Right ventricular and atrial pressure curves at rest from patient (SG) with tricuspid stenosis and insufficiency and atrial fibrillation. Functional diastole set-off between vertical lines. Note pressure in atrium increases during ventricular systole in a peak-plateau manner characteristic of tricuspid insufficiency. Mean resting gradient of 11.9 mm. Hg was largest in series.

FIG. 5 *Bottom.* Tracings from SG (fig. 4) redrawn and superimposed. Gradient is largest during early portion of diastole. Functional diastole begins during isometric relaxation and ends during isometric contraction. Note increase in pressures during exercise.

tricular systole before the completion of atrial systole (figs. 2 and 3).

Atrial Dynamics

The atrial contraction waves in tricuspid stenosis have been among the highest recorded in this laboratory. In the initial study of FC the pressure of 14 mm. Hg attained during atrial contraction was only 1 mm. less than the peak pressure of right ventricular systole (figs. 2 and 3). With exercise, atrial systole increased to 21 mm. Hg and ventricular systole to 23 mm. In the other patients with sinus rhythm, atrial systolic pressures of 13 to 21 mm. at rest and 16 to 23 mm. with exercise were recorded.

In only 1 of the 5 patients with normal rhythm was the so-called atrial C-wave usually attributed to valve closure noted. In another, this wave was present when the catheter tip was near the tricuspid valve only, and disappeared as the catheter was withdrawn into the atrium, suggesting that the wave was due to the valve leaflets impinging on the catheter tip rather than to a true change in atrial pressure during valve closure.

In the presence of normal sinus rhythm the atrial V-wave was very small, but the fall in atrial pressure when the tricuspid valve opened appeared to be normal. The rate of decline of the regurgitant wave in those patients with associated insufficiency did not differ sufficiently from that observed in the control series to be useful as a criterion of tricuspid stenosis.

Tricuspid Orifice Area

The calculated area of the tricuspid orifice ranged from 0.7 to 1.7 cm.^{2} in the 5 patients with normal sinus rhythm (table 2). The areas calculated at rest and during exercise checked within 0.2 cm.^{2} Tricuspid valvuloplasty was performed on FC, in whom the calculated area was 1.1 cm.^{2} At operation an experienced cardiac surgeon estimated the area as "not more than 1 square centimeter."

Less reliance can be placed upon the valve areas in patients with associated tricuspid insufficiency, since the rate of regurgitant flow and therefore the total forward flow across the valve are not known. Tricuspid valvuloplasty was recommended and performed in SG because the clinical and hemodynamic observations indicated a predominant tricuspid stenosis and the calculated area of 0.6 cm.^{2} was therefore considered reasonably reliable. At operation the valve area was estimated by the surgeon to be between 0.5 and 1.0 cm.^{2} and only a slight regurgitant stream was noted.

The cardiac output at rest was reduced in all but 1 patient (table 1). The single exception, JP, was 14 weeks pregnant at the time of study. Although her output was within the accepted normal range, it may possibly be abnormal when compared to the reported values for the first trimester of pregnancy.[7] The increase in cardiac output with exercise was subnormal for the degree of work per-

formed, as judged by oxygen consumption,[8, 9] in all but 1 patient, EH.

There was a significant correlation (r = 0.90, $p < .01$) between tricuspid valve area per square meter of body surface and the cardiac index (fig. 8). The data include those patients who had evidence of tricuspid insufficiency on the atrial pressure curve. This good correlation may indicate either that these patients had relatively little insufficiency, so that the valve area calculations were reasonably accurate, or that the valve area as calculated gives a good estimate of the reduction in output secondary to combined tricuspid stenosis and insufficiency. The correlation was less significant (r = −0.5 or less) when the valve size per square meter was compared to each of the following variables: mean gradient, log of the mean gradient, right atrial mean pressure, and right atrial mean pressure during ventricular diastole.

Associated Hemodynamic Abnormalities

The associated abnormalities delineated by cardiac catheterization were to a large extent a reflection of the accompanying multivalvular

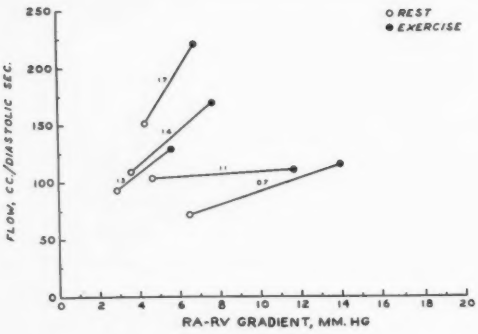
TABLE 2.—*Data Pertaining to Pressure Gradients in mm. Hg, Flows and Valve Areas in Ten Patients with Tricuspid Stenosis*

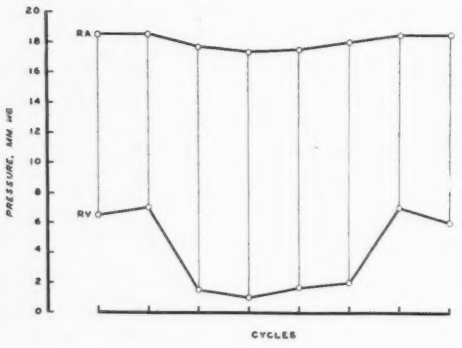
Patient	State	Atrial diastolic mean	Ventricular diastolic mean	Atrioventricular gradient	Flow, ml./diastolic sec.	Tricuspid valve areas cm.²	Ventricular end-diastolic	Atrial Z point RVed difference
F. C.	R	6.3	1.6	4.7	103	1.1	3.2	1.1
	E	13.2	1.5	11.7	160	1.1	1.0	8.4
F. C.*	R	9.5	5.4	4.4	81	0.9	6.6	−2.9
	E	15.5	6.5	9.0	174	1.3	1.1	6.6
E. R.	R	8.6	2.1	6.5	73	0.7	4.2	2.0
	E	17.6	3.6	14.0	115	0.7	2.6	16.7
R. P.	R	5.8	2.9	2.9	93	1.2	1.8	3.2
	E	8.7	3.1	5.6	129	1.2	2.7	0.9
J. P.	R	7.4	3.8	3.6	108	1.5	4.2	0.2
	E	12.1	4.4	7.7	169	1.3	3.4	9.4
E. H.	R	11.2	6.9	4.3	151	1.7	5.6	2.6
	E	11.5	4.7	6.8	220	1.7	8.0	4.8
S. G.	R	21.2	9.3	11.9	121	0.6	7.1	12.7
	E	30.4	11.2	19.2	—	—	11.2	17.6
R. R.	R	12.0	5.4	6.6	106	1.0	9.0	3.5
R. R.*	R	17.0	7.8	9.2	119	0.9	10.8	6.0
A. N.	R	17.6	11.0	6.6	132	1.2	12.6	4.4
L. R.	R	10.8	4.2	6.6	158	1.4	8.4	3.2
	E	15.7	8.0	7.7	—	—	11.5	3.8
J. F.	R	8.6	3.5	5.1	78	0.8	4.5	2.1
J. F.*	R	12.3	7.8	4.5	84	0.9	10.0	1.3

* Second study R: Rest E: Exercise

TABLE 3.—*Hemodynamics in Tricuspid Stenosis: Comparison of Eight Patients with Pure Mitral Stenosis and Normal Rhythm to Three Patients with Mitral and Tricuspid Stenosis and Normal Rhythm*

	Mitral stenosis mean ± S.D.	Mitral and tricuspid stenosis (mean ± S.D.)	Significance of difference between means (p)
Mitral valve area, cm.²/M.² B.S.A.	0.72 ± 0.02	0.72 ± 0.01	—
Cardiac output, L./min./M.² B.S.A.	3.03 ± 0.54	2.35 ± 0.83	$<.05 > .02$
Cardiac output, ml./diastolic sec./M.² B.S.A.	90 ± 13	62 ± 17	$<.01$
Pulmonary artery mean pressure, mm. Hg.	35 ± 5.5	16.3 ± 4.0	$<.01$
Pulmonary "capillary" mean pressure, mm. Hg.	23 ± 2.5	12.3 ± 3.2	$<.01$
Pulmonary vascular resistance, dynes-sec.-cm.$^{-5}$	270 ± 83	93 ± 40	$<.05 > .02$





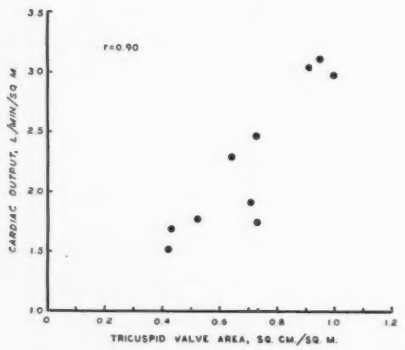


FIG. 6 *Top.* Relation between rate of blood flow (*ordinate*) and mean gradient (*abscissa*) across tricuspid valve at rest and during exercise in tricuspid stenosis. Calculated area of tricuspid orifice is included for each patient. In each instance gradient and flow increased during exercise.

FIG. 7 *Middle.* Variation during a respiratory cycle in mean diastolic gradient across tricuspid valve in patient (ER) with tricuspid stenosis. Points connected by a vertical line represent mean pressures (*ordinate*) in right atrium (*RA*) and ventricle (*RV*) for a single diastolic interval. Note relatively constant atrial pressure. During inspiration *RV* pressure falls and gradient increases; with expiration pressure rises and gradient decreases.

FIG. 8. *Bottom.* Relation between calculated tricuspid valve area per square meter (*abscissa*) and cardiac index (*ordinate*) in 10 patients with tricuspid stenosis. r = 0.90.

disease (table 1). Pulmonary "capillary" and arterial hypertension were present at rest or during exercise in all 9 patients with multivalvular disease. Pulmonary vascular resistance was normal in 5. Of the 4 patients with mitral stenosis as the only associated lesion 3 were in normal sinus rhythm and had mitral valve indices of 0.7 cm.^{2}/M.^{2} of body surface. These 3 patients were compared statistically to a series of 8 patients with a similar degree of mitral stenosis, normal sinus rhythm, and no other valvular involvement. The data, tabulated in table 3, demonstrate that the cardiac index, flow per diastolic second, pulmonary artery mean pressure, pulmonary "capillary" pressure, and pulmonary vascular resistance were significantly lower in the patients with stenosis of both mitral and tricuspid valves.

In patient SG, who had atrial fibrillation, a similar modifying effect of the tricuspid lesion on the hemodynamic alterations produced by mitral stenosis is apparent. She had less elevation of pulmonary vascular pressures and resistance than would be expected for the degree of mitral stenosis present (table 1).

Sequential Studies

Three patients were catheterized twice (tables 2 and 3). The data of RR obtained 39 months apart are virtually identical. In JF a 6-fold increase in pulmonary vascular resistance occurred in 29 months and pulmonary arterial pressure rose markedly although the cardiac index remained the same. This patient died 6 months after the second study and the clinical and hemodynamic diagnoses were confirmed at necropsy. In each of the 2 patients the estimated tricuspid valve orifice areas derived from the 2 different studies agreed within 0.1 cm.^{2} (table 2). Studies repeated on FC 13 months following tricuspid valvuloplasty revealed the functional orifice to be unchanged although at operation 1 commissure had apparently been fractured successfully. However, in contrast to the first study, cardiac output increased

appropriately with exercise. The elevated pulmonary "capillary" pressure present on the second study is interpreted as possible evidence of an elevated left ventricular diastolic pressure secondary to myocardial insufficiency, since the patient had no clinical or radiographic evidence of mitral or aortic valvular involvement.

Discussion

Physiologic Criteria for Diagnosis

Although the tricuspid valve is ideally located for study by catheterization of the right heart, there has not been agreement about the hemodynamic criteria for the diagnosis of stenosis of this valve. Ferrer and coworkers,[10] reporting 2 cases, emphasized the gradient across the valve at the onset of right ventricular systole. McCord, Swan, and Blount[11] reporting 3 cases, only 1 of whom had surgically significant stenosis, stated ". . . the increase in the early diastolic gradient is the most dependable hemodynamic characteristic of surgical tricuspid stenosis." In Gibson and Wood's study of 12 cases[12] the largest gradient across the valve at any moment during ventricular diastole was utilized as the evidence for stenosis.

On the basis of hydrodynamic principles Gorlin and Gorlin[6] have defined the variables that influence the flow of blood across stenotic valves. They clearly emphasized the importance of the *mean* pressure gradient across an obstructed valve and indicated its relationship to the rate of flow and the size of the orifice.

Use of the mean gradient *throughout* the period of ventricular filling as the criterion for the diagnosis of tricuspid stenosis avoids pitfalls inherent in emphasizing any single point on the pressure curves during ventricular diastole. An instantaneous gradient is not only subject to several limitations as a diagnostic criterion but cannot be related readily to other physiologic parameters. A gradient during early diastole is particularly unreliable, since a 3 to 4 mm. Hg difference between right atrium and ventricle at this point in the cardiac cycle has been noted in our laboratory in patients with rheumatic heart disease proved at autopsy not to have tricuspid stenosis. A similar difference between left atrial and ventricular pressures early in diastole has been observed in pure mitral insufficiency.[13] A gradient at the end of diastole (Z-RVed) greater than 1.2 mm. (2 standard deviations on the positive side of the mean value), as the control data from patients at rest indicate, would be unlikely in the absence of tricuspid stenosis; however, several patients in the present study had normal Z-RVed differences in spite of tricuspid stenosis. Any momentary gradient may be produced by artifacts, such as overshoot, in the recorded pressures. Such artifacts are minimized by integration of the pressures throughout diastole. Finally, in stenosis with atrial fibrillation a salient momentary gradient may be absent, despite a small but significant mean gradient.

When records are obtained and analyzed by the present method, a mean gradient greater than 1.9 mm. Hg at rest and 2.6 mm. during exercise (2 standard deviations on the positive side of the mean control value) would be most unlikely in patients with rheumatic heart disease without tricuspid obstruction. The gradients observed in tricuspid stenosis (table 2) are smaller than the left atrioventricular pressure differences noted in tight mitral stenosis,[5] which is usually associated with a pulmonary "capillary" pressure of around 28 mm. Hg[5] and a resulting gradient of 23 mm. (a left ventricular mean diastolic pressure of 5 mm. Hg is assumed). The largest resting gradient across the tricuspid valve in the present series was only 11.9 mm. Hg. The most obvious explanation for this difference is that the tricuspid orifices are larger than the mitral orifices. An additional factor is the lower cardiac output in tricuspid stenosis than in uncomplicated mitral stenosis (table 3). For any given degree of stenosis of an atrioventricular valve the smaller the blood flow the smaller the gradient across the valve.

Exercise provides an excellent test for evaluating a small resting gradient. There was some uncertainty about the significance of the 2.9 mm. Hg value in RP at rest, but the prompt rise to 5.6 mm. during exercise confirmed the

presence of tricuspid stenosis (fig. 6). The invariable increase in gradient is due to the augmentation of flow across the valve resulting from both the rise in cardiac output and the decrease in diastolic filling period that are associated with exercise. A greater pressure head is required to drive more blood in less time across the stenotic valve.

A stenotic atrioventricular valve, unlike the normal valve, probably opens during ventricular isometric relaxation and closes during ventricular isometric contraction. It is preferable to analyze the gradient throughout the period of functional rather than true diastole, which is set-off between the 2 points at which right atrial and ventricular pressures are identical (figs. 3 and 5). Sufficient cardiac cycles must also be analyzed to cover at least 1 complete respiratory cycle, since the gradient varies with alterations in intrathoracic pressure (fig. 7).

The accentuation of the murmur of tricuspid stenosis with inspiration, a phenomenon described by Rivero Carvallo,[14] is a reflection of the increase in gradient and flow that occurs with inspiration. In this lesion the right ventricular pressure follows the change in intrathoracic pressure (fig. 7), falling during inspiration and rising during expiration. The atrial pressure, however, remains relatively constant, probably because the increased venous return into the atrium with inspiration exceeds the augmented outflow across the stenotic valve. The change in the intensity of murmurs over the tricuspid area with respiration is a sign of cardinal diagnostic importance in patients with rheumatic heart disease.[3, 15]

The manner in which the gradient varied during the course of ventricular filling in atrial fibrillation and sinus rhythm was clearly reflected in the auscultatory phenomena.[3] The thrills and murmurs over the tricuspid area in atrial fibrillation were early and middiastolic; in normal sinus rhythm they were presystolic. During these phases of the cardiac cycle the gradients were maximal and were probably associated with greatest and most turbulent flow across the stenotic valve.

Critique of Orifice Calculation

Calculation of the functional orifice of the tricuspid valve by the formula of Gorlin and Gorlin[6] is useful in evaluating the degree of obstruction from a set of measured values for flow and gradient. Data are not available to determine precisely the correction factor for turbulence and orifice contraction needed in the calculation, but certain information suggests that the value of 1.0 as originally proposed[6] is satisfactory. Ferrer and co-authors[10] demonstrated that the area determined by planimetry of a scale postmortem photograph of the valve in a case of tricuspid stenosis agreed within 0.1 cm.^{2} of the calculated area. In the 2 patients from the present series who underwent tricuspid valvuloplasty and in the single case reported by Gorlin and Gorlin the calculated area agreed well with the estimate made from digital palpation by the surgeons, although it must be conceded that the surgeon's finger is not a precise planimeter.

The calculated area should be considered as a functional rather than an exact anatomic size, but this does not detract from the usefulness of the calculation by the Gorlin formula. Extensive experience has indicated that the formula frequently aids greatly in the preoperative and postoperative evaluation of patients with mitral stenosis. The data from the patients with tricuspid stenosis indicate its value in this lesion. The close correspondence between the areas at rest and during exercise (table 2) is impressive evidence of its reliability in relating flow and gradient to valve size. Without calculation of valve area it would be difficult to compare the physiologic data from one patient to the data from another or to compare repeated studies in the same patient. This is well illustrated by the postoperative study in FC (tables 1 and 2).

When there is associated tricuspid insufficiency, calculations of the orifice area yield falsely small values, since the rate of forward flow across the valve is greater than the cardiac output by an amount related to the regurgitant flow, which is unknown. When methods become available to measure the regurgitant flow,[16]

more precise estimations of the degree of stenosis and insufficiency will be possible.

Effects of Tricuspid Stenosis on Dynamics of Mitral Stenosis

The hemodynamic data of the 3 patients with combined mitral and tricuspid stenosis were significantly different from a group of patients with uncomplicated mitral stenosis of comparable severity (table 3). The lower pulmonary vascular pressures in the group with tricuspid stenosis are secondary to the lower flow and pulmonary vascular resistance. It is possible that the hemodynamic evidence of mitral stenosis might be obscured at rest by the effects of tricuspid stenosis. Such was the case in RP (table 1), in whom pulmonary venous hypertension was observed only during exercise. An important implication of these observations is that patients with tricuspid stenosis must be studied completely at rest and during exercise before the presence of significant mitral stenosis can be ruled out.

Major Hemodynamic Alterations

Tricuspid stenosis produces 2 major hemodynamic alterations, a reduction in cardiac output and an increase in right atrial pressure. Both these effects on cardiac function are of importance in the production of the major symptoms, fatigue and edema, and must be considered in attempts to define a "critical" area, if one exists, for the tricuspid valve.

The data from FC illustrate the ability of tricuspid stenosis alone to reduce cardiac output (table 1 and fig. 8). This reduction in output is due to the inability of the right atrium to propel blood past the obstructed valve at the normal rate. When tricuspid and mitral stenosis occur together, the cardiac output is lower than would be expected on the basis of the existing degree of mitral stenosis alone (table 3). The probable explanation is that the elevated pressure necessary to maintain flow across the obstructed mitral valve is created to a great extent by the pumping action of the right ventricle,[4] whereas only the right atrium performs this function for the tricuspid valve. In obstruction of the tricuspid valve, therefore, blood flow is limited proximal to the right ventricle. Restriction of blood flow at rest and during exercise is probably the outstanding factor responsible for fatigue. The regression formula derived from the data in figure 8 suggests that a tricuspid orifice smaller than 1.0 $cm.^2/M.^2$ of body surface may cause reduction of cardiac output. It would be of great interest to evaluate the pumping action of the right atrium by comparing the hemodynamic effects of normal rhythm and atrial fibrillation in a patient with tricuspid stenosis.

The level of atrial pressure in tricuspid stenosis is influenced by the diastolic pressure in the right ventricle, and the systolic insufficiency wave, if one is present, as well as by the gradient. The mean diastolic gradient depends on the flow per diastolic second and the valve size. At any particular rate of flow the smaller the orifice area, the larger is the gradient. Similarly for any given degree of stenosis, the larger the flow, the larger is the gradient.

Elevation of right atrial pressure and consequently of pressures throughout the systemic venous bed is a potent factor in the production of edema.[17-20] In this regard it is pertinent that the incidence of edema and ascites in patients with tricuspid insufficiency is 7 times greater when the right atrial mean pressure (measured in the edema-free state) is above 10 mm. Hg than when it is below this level.[1] Since the diastolic gradient across the stenotic valve is only 1 of the factors responsible for elevation of right atrial pressure, it is not possible to select a valve area that might be likely to be associated with edema, particularly in patients with multivalvular disease. However, if right ventricular mean diastolic pressure is normal (1–2 mm. Hg) and tricuspid insufficiency is not present, a right atrial pressure in excess of 10 mm. Hg would be required to maintain a normal resting output across a tricuspid orifice smaller than 0.7 $cm.^2/M.^2$ body surface or 1.3 $cm.^2$ for a patient of average size (1.7 $M.^2$).

Surgical Implications

A practical application of the hemodynamic data is in the selection of patients who may benefit from tricuspid valvuloplasty. The

importance of the mean diastolic gradient in the diagnosis of tricuspid stenosis by physiologic means has been emphasized and the range of gradient in the absence of tricuspid obstruction has been defined for this laboratory. Since absolute values will vary with the technics of study, the range of normal must be determined for the individual laboratory. If significant abnormalities in gradient and flow across the tricuspid valve are found, surgery may be indicated. In interpreting the data the influence of coexisting valvular lesions and the state of myocardial function must be considered. The final decision to perform surgery should be made only after a complete and multidisciplined clinical and hemodynamic appraisal of the patient.

Summary

Cardiac catheterization in 10 patients with tricuspid stenosis revealed an abnormal mean pressure gradient from right atrium to ventricle during ventricular diastole. The gradient was significantly in excess of the difference of -0.1 ± 1.0 mm. Hg at rest and $+0.5 \pm 1.1$ mm. Hg during exercise found in patients with rheumatic heart disease and no tricuspid stenosis. An elevated *mean* gradient, widening with exercise, was considered the most reliable physiologic criterion for the diagnosis of tricuspid stenosis.

The difference in pressures across the stenotic tricuspid valve increased with inspiration and decreased with expiration. It was largest during atrial contraction in normal sinus rhythm and early in diastole in atrial fibrillation.

The major effects of the lesion on the circulation were a restriction of cardiac output and elevation of right atrial pressure. The decrease in cardiac output correlated well with the degree of constriction of the tricuspid orifice as calculated by the formula for valve area. The cardiac output, pressures and resistance in the pulmonary vascular bed were lower in 3 patients with associated mitral stenosis when compared to a group of patients with a similar degree of mitral stenosis but no involvement of the tricuspid valve.

Acknowledgment

We are grateful to Mrs. Dolores Lukas Walker and Misses Elaine Hornberger and Loretta O'Neill for their technical assistance, and to Drs. Jorge Araujo, Gonzalo Sepulveda, Decio Penna, and Peter Mahrer who helped in the performance of the cardiac catheterizations.

Summario in Interlingua

Catheterisation cardiac in 10 patientes con stenosis tricuspide revelava anormal valores medie del gradiente de pression inter le atrio e le ventriculo dextere durante le diastole ventricular. Le gradiente excedeva significativemente le correspondente valor de $-0{,}1 \pm 1{,}0$ mm Hg in stato de reposo e de $+0{,}5 \pm 1{,}1$ mm Hg in stato de exercitio trovate in patientes con rheumatic morbo cardiac sed sin stenosis tricuspide. Un elevate valor *medie* del gradiente, crescente con exercitio, esseva considerate como le plus secur criterio physiologic in le diagnose de stenosis tricuspide.

Le differentia transvalvular del pressiones observate in casos de stenotic valvulas tricuspide se augmentava con inspiration e se reduceva con expiration. Illo esseva le plus pronunciate durante le contraction atrial in normal rhythmo sinusal e durante le prime phases diastolic in fibrillation atrial.

Le major effectos del lesion super le circulation esseva un restriction del rendemento cardiac e un elevation del pression dexteroatrial. Le reduction del rendimento cardiac esseva ben correlationate con le grado de constriction del orificio tricuspide calculate per medio del formula pro le area valvular. Le rendimento cardiac e le pression e resistentia in le vasculatura pulmonar esseva plus basse in 3 patientes con associate stenosis mitral que in un gruppo de patientes con simile grados de stenosis mitral sed sin affection del valvula tricuspide.

REFERENCES

[1] Sepulveda, G., and Lukas, D. S.: The diagnosis of tricuspid insufficiency: Clinical features in 60 cases with associated mitral valve disease. Circulation **11:** 552, 1955.

[2] Muller, O., and Shillingford, J.: Tricuspid incompetence. Brit. Heart J. **16:** 195, 1954.

[3] KILLIP, T., III, AND LUKAS, D. S.: Clinical features of tricuspid stenosis. To be published.

[4] LUKAS, D. S., AND DOTTER, C. T.: Modifications of the pulmonary circulation in mitral stenosis. Am. J. Med. **12:** 639, 1952.

[5] ARAUJO, J., AND LUKAS, D. S.: Interrelationships among "pulmonary capillary" pressure, blood flow and valve size in mitral stenosis. The limited regulatory effects of the pulmonary vascular resistance. J. Clin. Invest. **31:** 1082, 1952.

[6] GORLIN, R., AND GORLIN, S. G.: Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. Am. Heart J. **41:** 1, 1951.

[7] BADER, R. A., BADER, M. E., ROSE, D. J., AND BRAUNWALD, E.: Hemodynamics at rest and during exercise in normal pregnancy as studied by cardiac catheterization. J. Clin. Invest. **34:** 1524, 1955.

[8] FERRER, M. I., HARVEY, R. M., CATHCART, R. T., COURNAND, A., AND RICHARDS, D. W.: Hemodynamic studies in rheumatic heart disease. Circulation **6:** 688, 1952.

[9] DONALD, K. W., BISHOP, J. M., CUMMING, G., AND WADE, O. L.: The effect of exercise on the cardiac output and circulatory dynamics of normal subjects. Clin. Sc. **14:** 37, 1955.

[10] FERRER, M. I., HARVEY, R. M., KUSCHNER, M., RICHARDS, D. W., AND COURNAND, A.: Hemodynamic studies in tricuspid stenosis of rheumatic origin. Circulation Research **1:** 49, 1953.

[11] MCCORD, M. C., SWAN, H., AND BLOUNT, S. G.: Tricuspid stenosis: clinical and physiologic evaluation. Am. Heart J. **48:** 405, 1954.

[12] GIBSON, R., AND WOOD, P.: The diagnosis of tricuspid stenosis. Brit. Heart J. **17:** 552, 1955.

[13] FOX, I. J., WAKAI, C. S., CONNOLLY, D. C., AND WOOD, E. H.: Left atrial and ventricular pressure pulses in mitral valvular disease. Proc. Staff. Meet., Mayo Clin. **31:** 126, 1956.

[14] RIVERO CARVALLO, J. M.: Signo para el diagnostico de las insuficiencias tricuspideas. Arch. Inst. cardiol. México **16:** 31, 1946.

[15] CARRAL, R., AND DE TERESA: Diagnostico de las alteraciones tricuspideas. Rev. españ. cardiol. **3:** 375, 1949.

[16] KORNER, P. I., AND SHILLINGFORD, J. P.: The quantitative estimation of valvular incompetence by dye dilution curves. Clin. Sc. **14:** 553, 1955.

[17] BLAKE, W. D., WEGRIA, R., KEATING, R. P., AND WARD, H. P.: Effect of increased renal venous pressure on renal function. Am. J. Physiol. **157:** 1, 1949.

[18] FARBER, S. J., BECKER, W. H., AND EICHNA, L. W.: Electrolytes and water excretions and renal hemodynamics during induced congestion of the superior and inferior vena cava of man. J. Clin. Invest. **32:** 1145, 1953.

[19] WILKINS, B. A., JUDSON, W. E., AND BURNETT, C. H.: The effect of venous congestion of the limbs upon renal clearances and the excretion of water and salt. I. Studies in normal subjects and in hypertensive patients before and after splanchnicectomy. J. Clin. Invest. **32:** 1101, 1953.

[20] FITZHUGH, F. W., MCWHORTER, R. L., HARVEY, E., WARREN, J. V., AND MERRILL, A.: The effect of application of tourniquets to the legs on cardiac output and renal function in normal human subjects. J. Clin. Invest. **32:** 1163, 1953.

Science has taught to me the opposite lesson. She warns me to be careful how I adopt a view which jumps with my preconceptions, and to require stronger evidence for such belief than for one to which I was previously hostile.—HUXLEY.

Shoulder-Hand Syndrome Following Myocardial Infarction with Special Reference to Prognosis

By JOSEPH EDEIKEN, M.D.

Shoulder-hand syndrome occurs in approximately 10 to 15 per cent of patients following acute myocardial infarction. Sympathectomy, sympathetic block, cortisone, and various other therapies have been advocated. In the present communication the results of simple measures such as local heat, analgesics, and the regimen of active use of the affected extremity are described in treating 47 attacks in 42 patients with acute myocardial infarction.

IN 1936 we reported 14 patients who developed persistent pain in the shoulder region following myocardial infarction.[1] In 1941 Askey[2] studied a similar but larger group and described pain, swelling, and stiffness of the hands in addition to the shoulder symptoms. There have been a number of other reports[3-19] upon the shoulder-hand syndrome, many of them discussing sympathectomy, sympathetic block, and cortisone, with or without physiotherapy. In most of these publications the postinfarction cases were not separated from those following trauma or hemiplegia or due to diffuse vasculitis, cervical arthritis, or panniculitis.

In 1947, Steinbrocker,[6] describing predominantly advanced and severe cases, observed 3 stages in the evolution of the shoulder-hand syndrome. In the first, which lasted from 3 to 6 months, the patient experienced pain, tenderness, and limitation of motion at the shoulder girdle. Swelling, pain, stiffness, and discoloration of the hands and fingers usually followed, although the sequence is variable and both may occur simultaneously and gradually. In the second stage, which also lasted from 3 to 6 months, the shoulder pain and the hand swelling and discoloration gradually disappeared but the stiffness and flexion deformity of the fingers became more prominent and manifestations similar to Dupuytren's contracture began to appear. The third stage, which may last for months or become irreversible, is characterized by progressive atrophic changes in the hands, severe atrophy of the interosseous muscles, and limitation in motion at the metacarpophalangeal and interphalangeal joints. Contracture of the flexor tendons often occurs at this stage, particularly on the ulnar side, and rolling up of the palmar and digital fascia, in many ways similar to Dupuytren's contracture, is common. Occasionally a trigger zone may be present near or on the shoulder, pressure over which causes an increase in pain, suggesting the possibility that it may also be a manifestation of the syndrome. In 1936 we mentioned 2 cases with trigger zones.[1]

The present report is founded upon the study of 42 patients who developed symptoms of shoulder-hand syndrome after myocardial infarction. Of this group 32 were men and 10 women. The youngest was 38 years of age; the oldest, 73. These patients received no therapy except local heat, analgesics, and a regimen of active use of the affected extremity. It is hoped that the information gained may be a useful guide to prognosis for those patients who do not or cannot receive other forms of therapy, or for whom other treatment has not been completely successful, and that it may also serve as a standard against which the effectiveness of a specific therapy may be assessed. Our results indicate that this disorder, managed simply, is essentially self-limited and is usually less severe than might be inferred from some of the reports in the literature.

MATERIAL

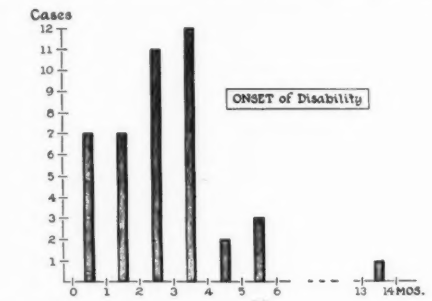
This study is based upon 42 patients who suffered 47 attacks of myocardial infarction. Shoulder-hand syndrome followed in 43 instances. In all, the diagnosis of myocardial infarction was made on the basis of a typical history and clinical course. In 33, the diagnosis was unequivocally confirmed by

From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

electrocardiogram; the infarction was anteroseptal in 1, anterior in 16, and posterior in 16. In the remaining 14 instances the electrocardiograms were invariably abnormal, but showed only persistent T-wave changes, which some physicians would interpret as indicative of ischemia without infarction. One patient had 2 attacks, both involving the anterior wall of the left ventricle. Another suffered an anterior infarction and, 6 months later, a posterior infarction. One case had 3 attacks, the first involving the anterior wall of the left ventricle, the second a posterior infarction 3 years later, and the third, 1 year afterward, a recurrent posterior infarction. Another patient had first a posterior infarction, then, 2 years later, an anterior infarction.

Onset. The earliest onset occurred 2 weeks after the attack of myocardial infarction. The majority took place within 4 months. Two occurred 5 months after the attack; 4, 6 months afterward; and 1 was delayed for 14 months. The time intervals are shown in figure 1.

Duration. Twenty-nine patients, the majority, obtained complete relief within 8 months after the onset of the shoulder-hand syndrome. Nine other attacks (1 patient recovered from 2) were relieved after 10 to 17 months. For 1, the duration was 22 months, and for 2 others, 2 years. One case having a trigger zone over the upper left chest anteriorly has not obtained relief after 3 years; pressure over his trigger zone produces severe pain radiating to the mid-chest and down the left arm. Another patient still has finger stiffness and pain 27 months after his infarction. Since the onset of his disability 4 weeks after a posterior infarction, he has had several periods of complete relief from the syndrome followed by recurrences in one or the other shoulder or hand. He has also had a Dupuytren-like contracture that has greatly improved but has not disappeared. During this time, although he has shown no clinical or electrocardiographic evidence of a recurrent infarction, he has had varying degrees of congestive heart failure. In figure 2 is illustrated the varying durations of disability for the entire group of patients.



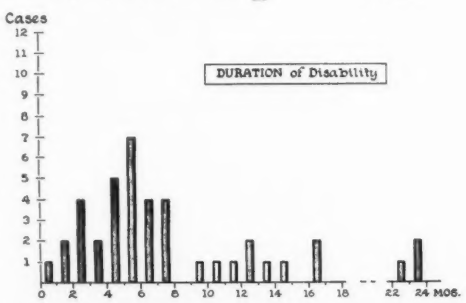


FIG. 1. Top. Onset of shoulder-hand syndrome in 43 instances following myocardial infarction; 1 patient suffered 2 attacks subsequent to repeated myocardial infarctions.

FIG. 2. Bottom. Duration of disability of the 41 instances of spontaneous relief.

Parts Involved. In this syndrome, one or both shoulders may be involved, one shoulder may improve only to have the other shoulder affected, or the shoulders may be involved alternately with frequent recurrences. The hands may be affected in several ways, the most common being stiffness of the fingers of one or both hands. The stiffness may improve in one hand only to become worse in the other, or both hands may improve and then suffer recurrences. In the most severe cases, a condition simulating Dupuytren's contracture may occur. In only 1 of our present group was there marked erythema of the thenar and hypothenar eminences; but we have observed this condition a number of times in patients outside this group.

Severity. In only 5 of our 42 patients did the disability reach the third stage described by Steinbrocker,[6] and the "claw hand"[9] was not seen in any of them. All the abnormalities of Steinbrocker's stages 1 and 2 were uncommonly seen in any 1 patient. In some instances pain in only one or both shoulder regions, or pain or stiffness of one or both hands, was present, often without any objective signs. In 11 instances, both shoulders and both hands were involved. In 12, one or both hands but neither shoulder, and in 8, one or both shoulders but neither hand was affected. In the remaining 12 instances there were various combinations of shoulder and hand involvement. In 1 of the 5 patients having Dupuytren-like contracture, the contracture had been present before the coronary occlusion and persisted after it. In 3 of the remaining 4 patients, the contracture decreased until cure seemed almost complete; in the other, the contracture persisted, though somewhat decreased, for 27 months. One patient had a condition resembling Dupuytren's contracture after the first myocardial infarction. After 2 years the contracture was considerably improved; but 17 months later, when she suffered another infarction, the contracture recurred but improved after 1 year.

Correlation of Syndrome with Location and Severity of Myocardial Infarction

We failed to detect any relationship between the transmission of the cardiac pain to the shoulders during the acute attack and the development or location of pain of the shoulder-hand syndrome. Shoulder-hand syndrome occurs in a small percentage (probably not more than 10 to 15 per cent) of cases of myocardial infarction, but the occurrence of the syndrome does not appear to follow recurrent coronary occlusion in any set pattern. For example, one patient remained free of symptoms suggesting the shoulder-hand syndrome after her first coronary attack in 1948; but following her second attack in 1951 she suffered a rather severe shoulder-hand syndrome, only to be free of any such symptoms after her third coronary attack in 1952. Another had an anterior infarction in 1952 and 4 weeks later marked finger stiffness ensued; but following a posterior infarction in 1953 she had neither shoulder pain nor any exacerbation of finger stiffness. One patient suffered stiffness of the fingers and Dupuytren-like contracture after each of her 2 coronary attacks, but her shoulders were never affected. Furthermore, in none of our 42 cases could the severity of the shoulder-hand syndrome be directly related to the severity, the extent, or the location of the myocardial injury. Some of our worst and most persistent cases followed a mild coronary attack in which the electrocardiogram showed no Q waves but merely T-wave changes in the precordial leads that disappeared long before the shoulder-hand syndrome cleared.

Cause of Syndrome Following Myocardial Infarction

The cause of this syndrome is not definitely known. In 1936[1] we suggested that it might be due to causalgia resulting from nerve fibers being caught in the cardiac scar. An analogous process has been described by Leriche[20, 21] in which periarterial sympathetic nerves are caught in scars of peripheral vessels. It has further been postulated that the afferent stimuli from the nerves cause widespread disturbances in the internuncial pool of the gray matter of the spinal cord. The possible value of sympathectomy was considered in our 1936 report.

The accidental inclusion of sympathetic fibers in the scar tissue might explain why only a small percentage of patients develop the syndrome after coronary occlusion, why it may take weeks or months to develop, and why in the same individual it may occur after one attack and not after another; it might also explain the absence of relationship between the severity of the syndrome and the severity and extent of the myocardial infarction.

Ernstene and Kinell[4] suggested that the symptoms of shoulder-hand pain following myocardial infarction may develop merely as the result of relative disuse of the shoulder and abnormal tension of the muscles of the shoulder girdle. It is recognized that the pain, the hand contracture, and in general the late symptomatology may be increased by disuse of the shoulder from immobilization in bed, or by the patient's fear that the shoulder pain may mean further myocardial damage. Nevertheless, in this author's opinion, the syndrome appears to be founded upon a complex neurogenic basis.

Discussion

Analysis of our data indicates that the prognosis in shoulder-hand syndrome following coronary occlusion is fairly good, with or without treatment, and that the syndrome is usually self-limited.

In recent years a number of reports[6-9, 11-19] have appeared in the literature concerning the efficacy of therapy, in particular of cortisone, sympathectomy, and sympathetic block; the results in general were considered good. We have used cortisone in many patients other than those included in the present study, and in a number of instances the symptoms were relieved; however, in our opinion cortisone did not shorten the course of the disability, and recurrences were quite frequent. Moreover, some cases of shoulder-hand syndrome are not relieved by cortisone, sympathetic block, or sympathectomy. Cortisone may be inadvisable where there are signs of congestive heart failure, and sympathectomy may properly be considered too hazardous in many cases. However,

the material in this study is offered because of its possible value in estimating the long-term prognosis.

None of the 42 patients (43 attacks of the syndrome) received any treatment except heat, analgesics, and exercise of the affected extremity, but only 2 failed eventually to be completely or almost completely relieved (fig. 2). One of these cases who had obtained no relief after 27 months, had both shoulders and both hands involved, the pain seeming to alternate from shoulder to shoulder and hand to hand. Hospitalization was refused and, because of symptoms of congestive failure, including nocturnal dyspnea, cortisone was not given. The other unrelieved patient, having suffered a posterior infarction 5 years previously, had a trigger zone remaining in the upper left chest anteriorly; pressure upon it produced pain that radiated to the sternum and down the left arm. In our experience the prognosis is poor for patients who have a trigger zone, although Steinbrocker[6] suggested that local injection of procaine into the sensitive area may be of benefit in some cases. Berger[22] reported favorable results from the injection of hydrocortisone. In 1936[1] we mentioned 2 patients with trigger zones in both of whom the results were poor, the syndrome persisting in 1 patient until his death 20 years after the original posterior infarction.

Before cortisone was available we observed a great many patients (none of them included in this series) who recovered from the shoulder-hand syndrome following myocardial infarction after times varying from a few months to several years. It has been our practice to induce these patients to exercise their painful shoulders by "climbing doors" with their arms and increasing abduction gradually; those who have stiff painful fingers are directed to squeeze a rubber ball under hot water. We have not observed that the original pain of the shoulder-hand syndrome is associated with stiffness of the shoulder joint. In some patients the onset of the syndrome is so gradual that they neglect to mention the pain but unconsciously immobilize the joint; others, assuming the pain is of coronary origin, fear to move the painful shoulder. Thus we have made it our regular practice to instruct all patients with coronary occlusion to move their arms and shoulders while in bed and to rest their heads on their hands for 15 to 20 minutes 3 or 4 times daily. Since the establishment of this regimen we have seen the severe types of shoulder-hand syndrome infrequently and the "claw hand" not at all. Of course care should be taken to exclude those patients who have developed a shoulder-hand syndrome following a cerebral accident where paralysis of the extremity may exist.

Summary

Complete or almost complete relief was obtained in 41 out of 43 attacks (95 per cent) of the shoulder-hand syndrome following coronary occlusion in 42 patients. These 42 patients received no treatment other than local heat, analgesics, and exercise of the shoulder and hand. The onset of the disability occurred from 4 weeks to 14 months (the majority within 4 months) after the coronary attack. Relief was obtained in 1 to 24 months (majority within 8 months) after onset. One or both shoulders may be involved and, in most cases, one or both hands also. In some only the shoulders, in others only the hands, were affected.

No direct relationship could be established between the location, severity, or extent of the myocardial injury and the onset, duration, and severity of the shoulder-hand disability. Some of the most obstinate disabilities occurred in patients whose myocardial lesion was considered minor. The involved shoulder may not be the one to which the cardiac pain was originally referred.

Immobilization of shoulder and fingers after onset of the syndrome (usually because the patient fearfully assumes it indicates more coronary damage) seems to increase the severity and duration of the disability, whereas movement in spite of the pain seems to decrease both.

Although some cases had severe pain and swelling of the hands, no instance of "claw hand" was observed in the 42 patients studied, or in the many other cases that have come under the author's observation.

Cortisone, sympathetic block, and sympathectomy have all been reported to be of value

in the treatment of the shoulder-hand syndrome following myocardial infarction and other causes. The present study, however, where the treatment consisted only of local heat, analgesics, and exercise, indicates that the shoulder-hand syndrome following coronary occlusion is a self-limited disability for which the prognosis is, in general, good. The regimen of exercise of the shoulders and fingers soon after the coronary attack and during the early stages of the syndrome increases the favorableness of prognosis.

Summario in Interlingua

Complete o quasi complete alleviamento esseva effectuate in 41 ex 43 attaccos (95 pro cento) de syndrome humero-manual post occlusion coronari in 42 patientes. Iste 42 patientes recipeva nulle tractamento excepte application local de calor, analgesicos, e exercitio del humero e del mano. Le declaration del invaliditate occurreva inter 4 septimanas e 14 menses (in le majoritate del casos intra 4 menses) post le attacco coronari. Le alleviamento esseva effectuate intra periodos de inter 1 e 24 menses (in le majoritate del casos intra 8 menses) post le declaration. Un sol o ambe humeros pote esser afficite; in le majoritate del casos etiam un o ambe manos. In alicun casos solmente le humeros es afficite; in alicun alteres, solmente le manos.

Nulle relation directe poteva esser establite inter loco, severitate, o magnitude del lesion myocardial e declaration, duration, e severitate del invaliditate humero-manual. Le plus obstinate invaliditates includeva alicunes in patientes con lesiones myocardial que habeva essite considerate como de severitate minor. Le humero afficite non es necessarimente le humero originalmente associate con le dolor cardiac.

Immobilisation de humero e digitos post le declaration del syndrome (usualmente effectuate per le patiente proque ille time que il se tracta de un signo de insulto coronari additional) pare augmentar le severitate e le duration del invaliditate, durante que movimento in despecto del dolor pare reducer ambes.

Ben que certe casos esseva characterisate per sever dolores e tumescentia del manos, nulle caso de "mano-falcula" esseva observate inter le 42 patientes studiate o inter le numerose altere casos que le autor ha habite le opportunitate de observar.

Cortisona, bloco sympathic, e sympathectomia ha omnes essite reportate como mesuras de valor in le tractamento de syndrome humero-manual post infarcimento myocardial e altere factores causal. Tamen, le presente studio—in que le tractamento consisteva exclusivemente de calor local, analgesicos, e exercitio—indica que le syndrome humero-manual post occlusion coronari es un invaliditate auto-restrictive in que le prognose es generalmente bon. Un regime de exercitios del humeros e digitos promptemente post le attacco coronari e durante le prime phases del syndrome mesme augmenta le character favorabile del prognose.

REFERENCES

[1] Edeiken, J., and Wolferth, C. C.: Persistent pain in the shoulder region following myocardial infarction. Am. J. M. Sc. **191:** 201, 1936.

[2] Askey, J. M.: The syndrome of painful disability of the shoulder and hand complicating coronary occlusion. Am. Heart J. **22:** 1, 1941.

[3] Leech, C. B.: Painful shoulder in association with coronary artery disease. Rhode Island M. J. **21:** 104, 1938.

[4] Ernstene, A. C., and Kinell, J.: Pains in the shoulder as a signal of myocardial infarction. Arch. Int. Med. **66:** 800, 1940.

[5] Johnson, A. C.: Disabling changes in the hand resembling sclerodactylia following myocardial infarction. Ann. Int. Med. **19:** 433, 1943.

[6] Steinbrocker, O.: The shoulder-hand syndrome. Associated painful homolateral disability of the shoulder and hand with swelling and atrophy of the hand. Am. J. Med. **3:** 402, 1947.

[7] —, Spitzer, N., and Friedman, H. H.: The shoulder-hand syndrome in reflex dystrophy of the upper extremity. Postgrad. Med. **3:** 359, 1948.

[8] —, —, and —: The shoulder-hand syndrome in reflex dystrophy of the upper extremity. Ann. Int. Med. **29:** 22, 1948.

[9] Hilker, A. W.: The shoulder-hand syndrome: A complication of coronary artery disease. Ann. Int. Med. **31:** 303, 1949.

[10] Carroll, I. N., and Mahru, M.: Shoulder-hand syndrome following coronary heart disease. Report of Case. Delaware State M. J. **22:** 52, 1950.

[11] Kammerling, E., Lewis, G. N., and Ehrlich, L.:

Recurrent post-infarctional shoulder-hand syndrome: Report of a case with unusual clinical evolution. New England J. Med. **242:** 701, 1950.

[12] SIGLER, J. W., AND ENSIGN, D. C.: ACTH and cortisone in the treatment of the shoulder-hand syndrome. Annual Meeting, American Rheumatism Association, Abstracts of Papers, June 8–9, 1951, p. 4.

[13] SWAN, D. M., AND MCGOWAN, J. M.: Shoulder-hand syndrome following myocardial infarction: Treatment by procaine block of the stellate ganglion. J.A.M.A. **146:** 774, 1951.

[14] KALSTONE, B. M.: Postcoronary syndromes. New Orleans M. & S. J. **104:** 708, 1952.

[15] RUSSEK, H. I., RUSSEK, A. S., DOERNER, A. A., AND ZOHMAN, B. L.: Cortisone in treatment of shoulder-hand syndrome following acute myocardial infarction. Arch. Int. Med. **91:** 487, 1953.

[16] STEINBROCKER, O., NEUSTADT, D., AND LAPIN, L.: Shoulder-hand syndrome: Sympathetic block compared with corticotropin and cortisone therapy. J.A.M.A. **153:** 788, 1953.

[17] LOSADA, L. M., AND ZANARTU, J.: Shoulder-hand syndrome. Rev. méd. de Chile **81:** 20, 1953.

[18] CRAIG, W. M., AND WITT, J. A.: Cervical disk, shoulder-arm-hand syndrome. Postgrad. Med. **17:** 267, 1955.

[19] MICHELE, A. A.: The conservative management of painful shoulder. New York State J. Med. **56:** 49, 1956.

[20] LERICHE, D.: De la sympathectomie peri-artérielle et de les résultats. Presse méd **25:** 513, 1917.

[21] —, AND STRICKER, P.: L'artériectomie dans les artérites obliterantes. Paris, Masson et Cie, 1933.

[22] BERGER, H.: Treatment of postmyocardial infarction shoulder-hand syndrome with local hydrocortisone. Postgrad. Med. **15:** 508, 1954.

WHY DO YOU SUPPORT THE AMERICAN HEART ASSOCIATION?

Comments upon Its Origin, Development, and Aims

From Address of Dr. H. M. Marvin before Officers of Affiliates of the American Heart Association, Monday Evening, October 29, 1956

. . . . . Having been involved in this great movement in a modest way for more than 25 years, it is not strange that I should have known many fine, dedicated people, a number of them sitting in this room, whose lives bear eloquent testimony to the truth of the prophetic words of Mrs. Browning: "The sick man thou hast served will make thee strong; the poor man thou hast served will make thee rich."

I know that many of you have found deep satisfaction in giving yourselves partly or wholly to unselfish efforts on behalf of those who are unfortunate, handicapped and sick. If there is anything more rewarding, except possibly ministering to man's spiritual needs, I have not heard of it. In a world filled with doubt, disappointment and failure, here is something to which sensitive people may turn in the full assurance of receiving great emotional rewards. William James once said, "The great use of a life is to spend it for something that outlasts it." He did not need to add that in spending it thus we can fill it with joy, with dignity, with precious memories; we can justify the qualities that make us human beings; we can in truth, add glory to our dust.

Let me ask, how many things do you know, subject to your control, which lift the heart and give wings to the spirit? How many do you know that deepen the significance of life and widen its horizons? How many do you know that bring joyous and abiding satisfaction? I can tell you one! It is participation in those activities which have as their aim the lessening of human suffering.

Disease of the Sinoatrial Node Associated with Bradycardia, Asystole, Syncope, and Paroxysmal Atrial Fibrillation

By R. I. Birchfield, M.D., E. E. Menefee, M.D., and G. D. N. Bryant, M.D.

Disease of the sinoatrial node due to coronary arteriosclerosis is rare. An unusual combination of arrhythmias attributed to disease of the sinus node and the effects of various pharmacologic agents, especially atropine, are described and discussed.

SINUS bradycardia has been associated with a number of entities, both normal and pathologic; however, it is usually of a transient nature. It has been found in 30 per cent of healthy young males,[1] the well-trained athlete,[2] and has been associated with pregnancy, particularly the post partum period.[3] Its incidence markedly exceeds what might be expected in starvation, myxedema, jaundice, increased intracranial pressure, beriberi, labyrinthitis, convalescence from certain infectious diseases, and bilateral thoracic sympathectomy.[4-6] In a series of 6,786 medical hospital admissions Kirk and Kuorning[5] found sinus bradycardia in 515 patients, or 7.6 per cent; syncope due to the sinus bradycardia occurred in only 1 patient. Sinus bradycardia due to arteriosclerotic heart disease is rare.

As can be seen from examination of the above list of entities, there are diverse causes of sinus bradycardia. These causes may be classified as neurogenic or non-neurogenic. By blocking of vagal activity with atropine increased vagal activity has been demonstrated in young men,[7] starvation,[4] and increased intracranial pressure.[8] Short[9] describes 4 patients with alternating sinus bradycardia associated with a variety of tachycardias. Sinus standstill was present in 2 patients and a wandering pacemaker in 3 patients. Atropine, effort, or emotion was found to accelerate the rate considerably, usually to a normal sinus rhythm, in all these patients.

Asystole with normal sinus rhythm and nodal rhythm have been described respectively by Laslett[10] and Wedd and Wilson.[11] These periods of asystole and concomitant syncope were ascribed to increased vagal tone and were abolished by atropine.

Non-neurogenic causes would include changes in the sinoatrial (S-A) node brought about by either the direct action of bacterial toxins, metabolic defects, or ischemic changes secondary to vascular disease. Winternitz and Selye[12] have reported a case of sinus bradycardia due to thrombosis of the artery to the sinus node.

Persistent sinus bradycardia that does not respond to exercise, emotion, or atropine is rare. Brasil[13] reported an organic sino-atrial depression, which did not respond to any of the above stimuli, in 13.5 per cent of 200 cases of Chagas' disease, and attributed this depression to a toxin from *Trypanosoma cruzi* that acted specifically on the sinoatrial node. The heart rate in these patients ranged between 50 and 70.

Pearson[14, 15] also reported a case of sinus bradycardia associated with asystole and syncope that failed to respond to exercise, atropine, and numerous pharmacologic stimuli.

In clinical practice, all the above bradycardias associated with asystole must be differentiated from the Adams-Stokes attacks, which occur in patients with any degree of atrioventricular block and in about 60 per cent of the patients with complete heart block; it should be kept in mind also that not all syncopal episodes associated with this entity are due to asystole, but to rapid ventricular arrhythmias as well.[16, 17]

The patient to be presented below has the outstanding features of the combination of sinus bradycardia, asystole with syncope, a

From the Department of Medicine, Duke University, Durham, N. C.

sinoatrial node unresponsive to atropine or other stimuli, and transient atrial fibrillation. Atropine had an interesting action on the atrioventricular (A-V node) but no demonstrable effect on the S-A node. We propose that organic disease of the S-A node probably secondary to coronary arteriosclerosis is the major factor in this case and, though vagal activity may be important in some of the attendant arrhythmias, it is not the cause of the persistent sinus bradycardia.

In publishing this case we repeat the remark of William Stokes, made 110 years ago, that "the observations are published with the view of drawing the attention of the Profession to a combination of cerebral and cardiac phenomena, of which our knowledge is still imperfect."[18]

Case Report

The patient, a 70-year-old white widow, entered the hospital on January 13, 1956, with the chief complaint of diplopia of 3 weeks' duration. There also was a history of bradycardia for 10 years and intermittent syncopal attacks for 5 years, with a recent increase in their frequency.

The diplopia first was noticed on waking, several days prior to Christmas, 1955; there were no other accompanying symptoms except for a slightly unsteady gait. Both symptoms disappeared whenever she looked to the left or covered either eye.

Ophthalmologic and neurologic examinations, including visual fields and skull x-rays, were normal. It was the neurologist's opinion that the diplopia was due to a right lateral rectus palsy secondary to thrombosis of a branch of the basilar artery.

Ten years ago a slow pulse rate of 40 was noted. Known hypertension had been present for the past 5 to 6 years, with blood pressures ranging between 200/120 to 245/140. Syncopal episodes began 5 years ago and occurred at 3- to 4-month periods until 18 months ago, when they became more frequent.

Twelve months ago she was hospitalized because of dyspnea and ankle edema; there was no chest pain. Following a prolonged period of bed rest and a regimen of diuretics and low-salt diet she improved, but since then had received diuretics intermittently because of recurrent ankle edema. She had not been digitalized.

Over the past year the syncopal attacks appeared on the wane, but 3 months ago increased in frequency with as many as 24 in a day. She had never fallen with these episodes, as there was a preceding aura of the sensation of blood rushing to her head and she either would sit or lie down quickly. Occasionally the periods of syncope would be preceded by a burst of rapid palpitations, then the heart would seem to stop and syncope would ensue. There was a tendency for the attacks to occur more frequently while the patient was lying down, rather than when sitting or moving about. The usual period of unconsciousness did not exceed 1 to 2 minutes by her estimation; often she awoke with a feeling of nausea, but within a few minutes was able to resume her work. A generalized nocturnal seizure occurred 3 years ago accompanied by urinary incontinence and a 20-minute period of unresponsiveness.

Significant in the past history were 2 separate episodes of thrombophlebitis with bilateral involvement of the legs.

On physical examination she appeared to be a pleasant, alert, cooperative, somewhat anxious, moderately obese woman. The positive findings included a paresis of the right lateral rectus muscle. Fundoscopic examination showed moderate arteriolar narrowing with minimal arteriovenous nicking, but no hemorrhages or exudates. Both carotid arteries were firm but pulsatile. The lungs were clear to auscultation and percussion. The left border of cardiac dullness extended almost to the left anterior axillary line, the cardiac rhythm appeared at times regular, at 32 per minute, but there were other periods of marked irregularity with occasional pauses up to 3 seconds in duration. The pulmonic second sound was increased and louder than the aortic and there was a diffuse, harsh, low-pitched, grade III systolic murmur, best heard over the aortic area that radiated toward the neck. The blood pressure was 180/80. Tender 2+ pitting pretibial edema was present almost to the knees. Neurologic examination, except for the right sixth cranial nerve palsy, was within normal limits.

The hemogram was normal, and urinalysis showed specific gravities of 1.010 to 1.018 on random samples and no abnormalities. The corrected sedimentation rate was 9 mm. per hour. Blood chemistry evaluations, including nonprotein nitrogen, cholesterol, and electrolytes, were within normal limits. The basal metabolic rate ranged from minus 19 to minus 7 per cent, the 24-hour radioiodine uptake was 10 per cent, and the protein-bound iodine was 5.2 μg. per cent. Chest x-ray showed that the heart was slightly enlarged to the left and the right hilum was prominent from what was thought to be a vascular shadow. The admission electrocardiogram showed a rate of 24 per minute, P-R 0.18 second, and QRS 0.06 second; it was interpreted as showing a marked sinoatrial bradycardia but otherwise to be within normal limits (fig. 1).

Mercuhydrin was given shortly after admission and a 1200-calorie, 35-Gm. fat, 400-mg. sodium diet was instituted along with bed or chair rest. The weight dropped from 81.75 Kg. to 77.95 Kg. in the first 24 hours, and the ankle edema disappeared in 2 to 3 days.

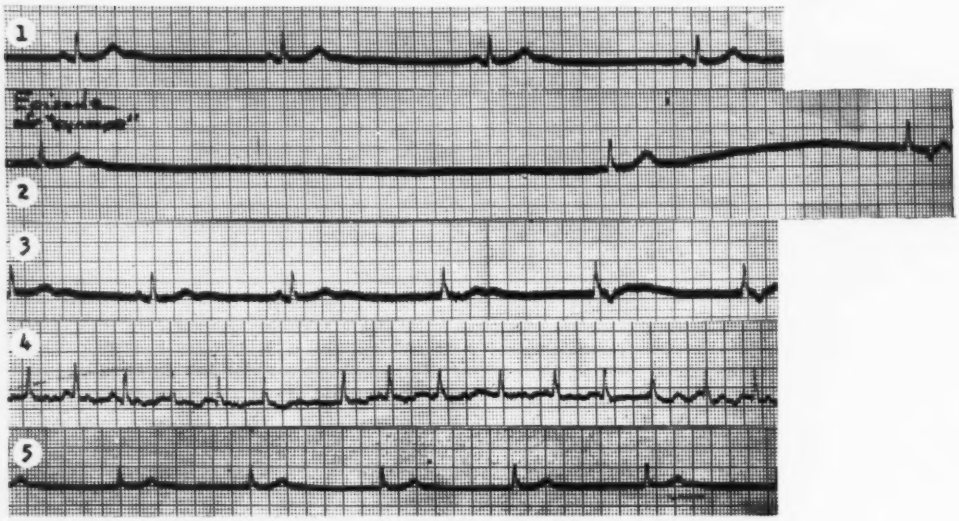


FIG. 1. Control electrocardiogram, sinus bradycardia at 26 per minute.

FIG. 2. Asystole of 6 seconds' duration resulting in syncope. Note recovery by a nodal beat.

FIG. 3. Conversion to a low nodal rhythm at 32 per minute, 90 seconds after atropine, 1.2 mg. intravenously.

FIG. 4. Paroxysmal atrial fibrillation at 110 per minute.

FIG. 5. Mid-nodal rhythm at 40 per minute after atropine, 2.0 mg. intravenously.

The patient continued to have syncopal attacks, which were heralded by a moan, facial pallor, and closing of the eyes. During the shorter periods of asystole she could hear but felt unable to move, and during the longer periods (9 seconds) minimal convulsive movements of the right arm were noted. The onset of syncopal symptoms occurred between 4.4 and 4.8 seconds after asystole (fig. 2).

On the fifth hospital day the electrocardiogram showed a sinus bradycardia with a rate of 26; however, the P-R interval varied between 0.18 and 0.12 second. Occasionally the P-R interval was at its shortest just before a period of asystole. Resumption of the heart beat after a period of asystole was invariably by a nodal beat followed by other irregular nodal beats and gradual return to a sinus bradycardia. Atropine, 1.2 mg. intravenously, was given after these observations. Ninety seconds after injection a nodal rhythm began with retrograde P waves at 32 beats per minute (fig. 3). After the atropine there were no syncopal attacks for 6 hours and numerous electrocardiograms taken during this time continued to show an A-V nodal rhythm with retrograde P waves. The only side effects were dryness of the mouth and mild blurring of vision; she expressed a preference for these symptoms to the syncopal attacks.

Seven hours after atropine sinus bradycardia again was present. After sitting up 8 times a slightly *irregular* nodal rhythm with intermittent retrograde P waves appeared, which reverted after 45 seconds to a sinus bradycardia at 28 per minute. Carotid sinus pressure was applied without any demonstrable effect. Methantheline bromide, 50 mg. orally, failed to abort the attacks that night and produced no changes in rhythm.

On the sixth hospital day, several periods of asystole were recorded and 100 mg. of methantheline bromide orally was followed in 35 minutes by an irregular rhythm with mixed sinus and nodal beats.

Asystole was not prevented, however, and 3 hours after methantheline bromide a sinus rhythm at 21 per minute was present. Exercise at this time produced a rate of 30 per minute, with P-R intervals varying between 0.18 and 0.10 second, and an occasional nodal beat; in the sitting position there was a change to a nodal rhythm with retrograde P waves at 29 beats per minute, and in the supine position there was a short burst of nodal bigeminy followed by a sinus beat, then asystole of 4.9 seconds accompanied by syncope.

The attacks of syncope continued during the evening and in the early morning of the seventh hospital day she noticed the onset of rapid palpitations. An electrocardiogram showed atrial fibrillation with a ventricular rate of 110 per minute and an isoelectric or inverted T wave in lead II (fig. 4). Ten hours after the onset of palpitations they terminated

suddenly and spontaneously, and were followed immediately by a period of syncope.

A midafternoon electrocardiogram showed a nodal rhythm at 24 per minute. Atropine, 2.0 mg. intravenously, increased the rate to 40 and the nodal rhythm without retrograde P waves persisted (fig. 5). Four hours later there was a nodal rhythm with retrograde P waves. Ephedrine, 15 mg. intramuscularly, was given whereupon nodal bigeminy mixed with a sinus bradycardia began 1 to 2 minutes later.

Twelve minutes later nodal tachycardia at 100 per minute was present, which was followed in sequence by a short burst of paroxysmal atrial tachycardia with varying degree of atrioventricular block, a 9-second period of asystole, and a nodal rhythm at 45 per minute. During the tachycardia there was inversion of the T wave in lead II.

On the eighth hospital day sinus bradycardia at 27 per minute again was present. Isopropyl norepinephrine, 10 mg. sublingually, was followed in 12 minutes by a nodal rhythm with retrograde P waves at 34 per minute; however, syncopal attacks continued.

Since atropine had provided the most symptomatic relief, it was given 1.5 mg. orally every 8 hours on the ninth hospital day. The syncopal attacks then occurred only in the few hours preceding each dose of atropine; the patient was given 1.5 mg. every 6 hours with considerable reduction in the number of attacks. She was discharged on the next day.

The patient continued to have syncopal attacks, but only in the sixth hour after atropine, so it was given every 5 hours.

She was seen on a clinic visit on April 4, 1956, and had had no further attacks after changing to the 5-hour schedule. She had gradually lengthened the interval between doses to 8 hours and still had not had another syncopal attack. The diplopia had cleared and she had resumed her normal activities, but was slightly bothered with a dry mouth, visual blurring, and constipation.

Physically she appeared much improved and had lost weight, from 81 to 68 Kg., the blood pressure was 160/90, and the heart was regular at 34 per minute. An electrocardiogram showed a wandering pacemaker with impulses arising from the S-A node and the A-V node with both high and low A-V nodal beats.

She remained symptom free until October 1956, when the syncopal attacks recurred 10 to 12 days after being started on reserpine and mecamylamine. These drugs were stopped on October 18 but the attacks continued over the next 4 days, requiring hospitalization. Over the next 5 to 6 days the attacks decreased and stopped on the sixth day. She was maintained on atropine 1.2 mg. every 5 hours, and when seen in the clinic in December 1956 had remained symptom free.

Discussion

In this patient the S-A node had been so altered that neither vagal nor sympathetic impulses had any effect on its rate. Atropine increased the irritability of the A-V node and allowed it to control the rate of the heart.

The vagus nerves have equally numerous endings in both the S-A and A-V nodes.[19] The heart rate is influenced by both the vagal and sympathetic nerves. The vagal influence is usually negated by giving atropine, 2 mg. parenterally; the usual response is an increase in heart rate of 37 to 42 beats per minute.[20] Vagal control over the heart also is lessened by exercise.[7]

The accelerating influence of the sympathetic nerves to the heart is shown by bilateral thoracic sympathectomy. Such patients have a resting bradycardia and acceleration of the heart rate is both delayed and lessened in response to exercise.[6] When patients with bilateral thoracic sympathectomy including the stellate and celiac ganglia are given atropine, the resultant resting heart rate is below that which is expected in normal persons.[21]

The failure of the sinus rate to increase in our patient after atropine points strongly to disease of the S-A node as the basis of the persistent bradycardia, rather than abnormal vagal activity. The nature of the disease involving the S-A node is unknown. The authors believe that there is sufficient clinical substrate to place coronary arteriosclerosis high on the list of suspected diseases.

Upon review of the literature, the mechanism of production of sinus bradycardia and accompanying periods of asystole is uncertain. Pearson[14, 15] has described a case very similar to ours and in his first article postulated that atheromatous embarrassment of the blood supply to the S-A node was the cause, but autopsy several years later failed to disclose any anatomic lesions, either gross or microscopic, of either sinus or the A-V nodes or any evidence of coronary arteriosclerosis. A bronchogenic carcinoma was found that involved the mediastinal structures but not the heart. Pearson did not believe that the tumor could impose a constant vagal stimulus without vagal escape.

Intermittent vagal stimulation by the tumor might account for the periods of asystole, but the failure of atropine to relieve the bradycardia or the periods of asystole cannot be explained by invoking vagal stimulation as the causative mechanism.

Pearson also reviewed the literature on similar arrhythmias, but could not find any conclusive evidence concerning their possible etiology.

Winternitz and Selye[12] describe a case of sinus bradycardia of sudden onset; at autopsy infiltration of lymphocytes, polymorphonuclear neutrophils, and plasma cells in the area of the sinus node and thrombosis of the artery to the S-A node were found. The patient's critical condition and early death apparently made clinical study of this bradycardia inopportune.

The periods of asystole related to the S-A node have at least 2 probable causes: either sinus arrest or sinoatrial block. Clinically, sinus arrest is associated with vagal reflexes such as can be induced by gagging or a hypersensitive carotid sinus. The usual measures used to induce vagal reflexes were without effect in our patient.

Sinoatrial block was reviewed briefly by Kisch and Zucker[22] in 1942 without definite agreement as to whether it is due to functional causes or pathologic lesions. They presented a case of sinoatrial block and retrograde atrial conduction associated with permanent complete heart block, and at autopsy there was moderate sclerosis of the coronary arteries, a scar in the upper portion of the intraventricular septum, and atrophy of the muscular tissue in the region of the A-V node. Friedberg[23] states that sinoatrial block usually is associated with digitalis or quinidine administration, or organic lesions involving the sinus node.

Electrocardiographically, sinoatrial block usually shows a prolonged P-P interval that approximates a multiple of the normal P-P interval; this phenomenon does not appear to be present in our case, but the moderate arrhythmia associated with the bradycardia and the fact that the beat was always resumed from an A-V nodal impulse makes this difficult to ascertain.

Experimental sinoatrial block with A-V nodal escape has been produced by Scherf.[24] In order to obtain rhythms with bradycardia or long periods of standstill he found it necessary to damage the sinus node and depress the A-V node as well. Complete severance of the vagi had no influence on these experiments.

A more definitive analysis of this type of rhythm will have to wait until either chance or ingenious technical development allows the use of fine exploring electrodes, such as used by Puech and co-workers[25] or Lanari, Lambertini, and Revin[26] on the human heart.

The chief therapeutic benefit derived from atropine in this case was the development of an A-V nodal rhythm. Wilson[27] produced A-V nodal rhythms with atropine; vagal stimulation after 1 mg. hypodermically slowed the S-A node and allowed the A-V node to serve as the pacemaker. This action of atropine depends on its abolishing vagal influences at the A-V node before affecting the sinus node; however, there is some evidence that atropine may affect the A-V node per se, independent of the release of vagal influence.[28] Our patient fortunately was relieved by the development of an A-V nodal rhythm; Pearson's case developed A-V nodal extrasystoles after atropine, but was not freed of syncopal attacks due to asystole.

The use of other drugs, including methantheline bromide, isopropyl norepinephrine, and ephedrine will not be discussed here; Haymond and Bellet,[29] and Nathanson and Miller[30] adequately described the actions of these drugs that might be expected to be of benefit.

It appeared that vagal activity was of importance in the production of syncope, since the A-V node still responded to vagal activity. Increasing vagal activity by lying down increased the frequency of the attacks, while decreasing vagal activity by standing or by atropine lessened the frequency of the syncopal attacks. Exercise also lessens vagal tone and in this patient produced a nodal rhythm.[7, 31] These vagal effects seemed not to operate at all through changes in the S-A node activity, but did determine how quickly the A-V node assumed control of impulse formation once sinus standstill had occurred.

Experimentally, atrial fibrillation is more

readily produced by acetylcholine after cooling the S-A node.[32] The episode of paroxysmal atrial fibrillation in our case draws an interesting but speculative parallel.

The duration of the syncopal attacks following the use of reserpine is compatible with its known period of activity. The relative parasympathetic predominance produced by reserpine accentuates the importance of autonomic activity in the production of asystole.

Due to the periodicity of the asystole, no claims can be made that atropine will continue to be as beneficial as apparently it now is. The necessary changes in the dosage schedule of the atropine serve to emphasize the waxing and waning influences that produce the asystole. The use of atropine appears well worth a trial in cases similar to this one.

Summary

The clinical picture produced by disease of the sinoatrial node is described and illustrated by a case report. Disease of the S-A node has been implicated as the cause of the persistent bradycardia. Autonomic influences over the A-V node have been implicated in the production of asystole. In this patient any maneuver decreasing vagal tone was of benefit because these circumstances allowed the rhythm of the heart to be controlled by the A-V node. Sitting up, exercise, and atropine were all effective means of initiating nodal rhythm.

Acknowledgment

The authors wish to acknowledge the constructive criticisms of Dr. Eugene Stead and to thank Dr. Ernst Peschel for help in translating the German articles.

Summario in Interlingua

Le tableau clinic de morbo del nodo sino-atrial es describite e illustrate per le reporto de un caso. Morbo del nodo sino-atrial ha essite implicate como causa del persistente bradycardia. Influentias autonome super le nodo atrio-ventricular ha essite implicate in le production de asystole. In le presente patiente omne manovra capace a reducer le tono vagal esseva benefic, proque sub iste conditiones le nodo atrio-ventricular poteva regular le rhythmo cardiac. Seder se erecte, exercitio, e atropina, omne istos esseva medios efficace pro initiar un rhythmo nodal.

References

[1] Packard, J. M., Graettinger, J. S., and Graybiel, A.: Analysis of the electrocardiograms obtained from 1,000 young healthy aviators. Circulation **10:** 384, 1954.

[2] White, P. D.: Extreme bradycardia (below the rate of 40) in athletes, especially distance runners. Letter, J.A.M.A. **120:** 642, 1942.

[3] Eastman, N. J.: Williams' Obstetrics. Ed. 10., Appleton-Century-Crofts, Inc., New York, 1952.

[4] Kerckhoff, K., and Stürmer, K.: Ueber die hungerbradykardie und ihre beeinflussung durch atropin. Med. Klinik **44:** 1119, 1949. *In* Abstracts of World Medicine **7:** 377, 1950.

[5] Kirk, J. E., and Kuorning, S. A.: Sinus bradycardia. A clinical study of 515 consecutive cases. Acta med. scandinav., Supp. **266:** 625, 1952.

[6] Chapman, E. M., Kinsey, D., Chapman, W. P., and Smithwick, R. H.: Sympathetic innervation of the heart in man, preliminary observations of the effect of thoracic sympathectomy on heart rate. J.A.M.A. **137:** 579, 1948.

[7] Robinson, S., Pearcy, M., Brueckman, F. R., Nicholas, J. R., and Miller, D. I.: Effects of atropine on heart rate and oxygen intake in working men. J. Appl. Physiol. **5:** 508, 1953.

[8] Campbell, G. S., Haddy, F. J., Adams, W. L., and Visscher, M. B.: Circulatory changes and pulmonary lesions in dogs following increased intracranial pressure and the effect of atropine upon such changes. Am. J. Physiol. **158:** 96, 1949.

[9] Short, D. S.: The syndrome of alternating bradycardia and tachycardia. Brit. Heart J. **16:** 208, 1954.

[10] Laslett, E. E.: Syncopal attacks, associated with prolonged arrest of the whole heart. Quart. J. Med. **2:** 347, 1908.

[11] Wedd, A. M., and Wilson, D. C.: Standstill of the heart of vagal origin. Am. Heart. J. **5:** 493, 1930.

[12] Winternitz, M., and Selye, H.: Ein fall von sinus bradykardie durch sinus-arterienthrobose. Wein, Arch. f. inn. Med. **16:** 377, 1929.

[13] Brasil, A.: Organic sino-auricular depression: A new disturbance of the cardiac rhythm. Fourth Inter-American Congress of Cardiology, Rev. argent. cardiol. **19:** 331, 1952. Abstracted, Circulation **8:** 625, 1953.

[14] Pearson, R. S. B.: Sinus bradycardia with cardiac asystole. Brit. Heart J. **7:** 85, 1945.

[15] —: Sinus bradycardia with cardiac asystole. Brit. Heart J. **12:** 61, 1950.

[16] Parkinson, J., Papp, C., and Evans, W.: The

electrocardiogram of the Stokes-Adams attack. Brit. Heart J. **3:** 171, 1941.

[17] PENTON, G. B., MILLER, H., AND LEVINE, S. A.: Some clinical features of complete heart block. Circulation **13:** 801, 1956.

[18] STOKES, W.: Observations on some cases of permanently slow pulse. Dublin Quart. J. Med. Sc. **2:** 73, 1846.

[19] STOTLER, W. A., AND MCMAHON, R. A.: The innervation and structure of the conductive system of the human heart. J. Comp. Neurol. **87:** 57, 1947.

[20] CRAIG, F. N.: Effects of atropine, work and heat on the heart rate and sweat production in man. J. Appl. Physiol. **4:** 826, 1952.

[21] GRIMSON, K. S.: Personal communication.

[22] KISCH, B., AND ZUKER, G.: Sinoauricular block and retrograde auricular conduction in a case of permanent complete heart block. Am. Heart J. **23:** 269, 1942.

[23] FRIEDBERG, C. K.: Diseases of the Heart. Philadelphia and London, W. B. Saunders and Company, 1949.

[24] SCHERF, D.: Experimental sinoauricular block. Proc. Soc. Exper. Biol. & Med. **61:** 286, 1946.

[25] PUECH, P., ESCLAVISSAT, M., SODI-PALLARES, D., AND CISNEROS, F.: Normal auricular activation in the dog's heart. Am. Heart J. **47:** 174, 1954.

[26] LANARI, A., LAMBERTINI, A., AND RAVIN, A.: Mechanism of experimental atrial flutter. Circulation Research **4:** 282, 1956.

[27] WILSON, F. N.: The production of atrioventricular rhythm in man after the administration of atropin. Arch. Int. Med. **16:** 989, 1915.

[28] GRANT, R. P.: The mechanism of A-V arrhythmias. Am. J. Med. **20:** 334, 1956.

[29] HAYMOND, T., AND BELLET, S.: Effect of banthine on the cardiac mechanism in states associated with increased vagal tone. Am. J. Med. **16:** 516, 1954.

[30] NATHANSON, M. H., AND MILLER, H.: The action of norepinephrine, epinephrine and isopropyl norepinephrine on the rhythmic function of the heart. Circulation **6:** 238, 1952.

[31] HELLEBRANDT, F. A., AND FRANSEEN, E. B.: Physiological study of the vertical stance of man. Physiol. Rev. **23:** 220, 1943.

[32] LOOMIS, T. A., AND KROP, S.: Auricular fibrillation induced and maintained in animals by acetylcholine or vagal stimulation. Circulation Research **3:** 390, 1955.

Medical Eponyms

By ROBERT W. BUCK, M.D.

Corrigan Pulse. Aortic regurgitation had been described by several physicians before the appearance of a communication by Dominic John Corrigan (1802–1880), Physician to the Charitable Infirmary of Dublin and Lecturer on the Theory and Practice of Medicine at St. Patrick's College, Maynooth, in the *Edinburgh Medical and Surgical Journal* 37: 225–245 (April 1), 1832, "On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves," but his account has become a classic.

"When a patient affected by the disease is stripped, the arterial trunks of the head, neck, and superior extremities immediately catch the eye by their singular pulsation. At each diastole the subclavian, carotid, temporal, brachial, and in some cases even the palmar arteries, are suddenly thrown from their bed, bounding up under the skin. . . . Though a moment before unmarked, they are at each pulsation thrown out on the surface in the strongest relief."

Acute Reversible Heart Failure in Africans

By H. Grusin, M.B., B.Ch., M.R.C.P. (Lond.)

Sixteen cases of acute reversible heart failure were observed in the native African. On the basis of their responses to dietary and vitamin therapy they were divided into various etiologic groups. The clinical manifestations are described and the relationship of these cases to idiopathic cardiac hypertrophy of Africans is discussed.

ACUTE reversible heart failure is common among Africans (Bantu) living in and around Johannesburg. In some cases the temporary heart failure is due to some obvious cause such as acute nephritis, anemia, diphtheria, or pulmonary embolism, but in many patients the etiology is obscure. Gillanders[1] described a type of heart disease that in its early stages could be reversed by an adequate diet, but usually progressed to chronic heart failure when the patient returned to his deficient home diet. Other types of heart failure are seen, however, that apparently disappear rapidly and completely (fig. 1). In this study a series of such cases has been collected and an attempt made to classify the various syndromes observed.

Material and Methods

The subjects of this study were Bantus living in or near Johannesburg. Like many of their kind they had subsisted for years on an inadequate diet containing small quantities of animal protein and fat and a high proportion of carbohydrate in the form of maize. Most were alcoholics who drank brandy and unmatured homemade brews known locally as "babaton" and "skokiaan." The following groups of patients were studied: 1. Sixteen successive cases of acute heart failure, i.e., patients with a short history who made a complete clinical and radiologic recovery within 3 to 4 weeks. Obviously many had to be judged retrospectively. 2. Ten cases of edema not due to renal or cardiac causes. 3. A control group of 7 cases of chronic, recurrent heart failure.

All patients were confined to bed; their weight and urinary output were recorded daily. They were maintained for 5 to 10 days on a diet low in thiamine content but adequate in other respects.* If they showed no clinical improvement on this regime, then vitamin B_1 was added for a further 5 to 10 days (thiamine hydrochloride 100 mg. twice a day intramuscularly). If there was still no response, digitalis and mersalyl were administered (tablets of digitalis leaf, 9 gr. daily for 3 days and 3 gr. daily thereafter; mersalyl 2 ml. intramuscularly on alternate days; ammonium chloride 15 gr. three times a day).

The rice was washed, boiled rapidly in 500 ml. of water for half an hour. After cooking it was strained and washed under running water until completely free of cooking water. It was divided into 3 equal portions for each of the 3 meals.

The meat used was thin cuts of sirloin steaks fried in a portion of the butter ration. Both rice and meat were reheated in steam ovens for 10 minutes before serving.

Canned peaches were drained of syrup and washed with cold running water. Dried peaches were washed and boiled rapidly for three quarters of an hour in water. The cooking water was drained off and the peaches were again washed under running water, reheated with additional water and sweetened with sugar. Desserts were prepared with either tapioca, sago or cornflour, sugar, butter, and water. They were flavored by caramelizing the sugar or by the use of commercial jelly crystals.

Weak tea with sugar but no milk was served with breakfast, midmorning, midafternoon, and supper meals.

Observations. On the basis of their response to these regimens the 16 cases of acute heart failure fell into the following groups (table 1): 1. Ten cases responded completely to thiamine (beriberi heart disease). 2. Three cases were unresponsive to thiamine (syndrome A). 3. Three cases responded completely on a thiamine-low diet (syndrome B).

From the Baragwanath Hospital and the University of the Witwatersrand, Johannesburg, South Africa.

* Diet consisted of raw edible weights of the following:

Rice (polished)	200 Gm.
Canned peaches	100 Gm.
Cheddar cheese	25 Gm.
Sugar and glucose sweets	160 Gm.
Tapioca, sago or cornflour	100 Gm.
Meat	100 Gm.
Dried peaches	100 Gm.
Butter	50 Gm.
Jelly (commercial jelly crystals)	60 Gm.
Ascorbic acid	0.05 Gm.
Halibut liver oil	0.2 ml.

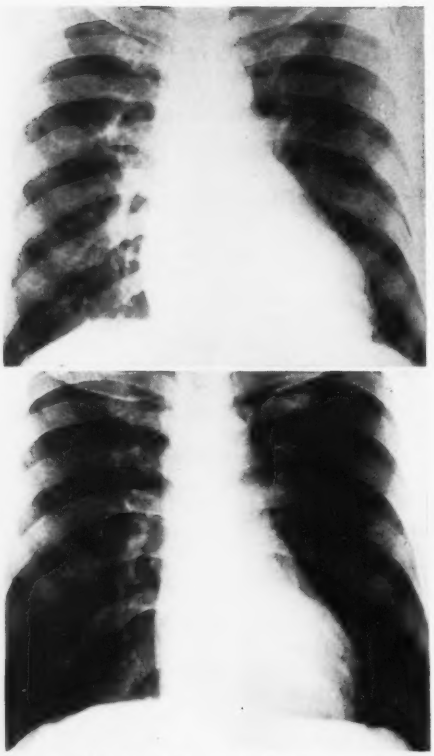


FIG. 1. *Top.* Acute heart failure. *Bottom.* The same patient 3 weeks later. Four years later the appearances were unchanged.

Clinical Features and Responses of Patients with Heart Failure

Controls. These consisted of 7 cases of chronic heart failure (2, rheumatic mitral stenosis; 2, syphilitic aortic incompetence; and 3, hypertension). On the thiamine-low diet or after thiamine was administered, 2 types of response were observed. Four patients lost no weight but the remaining 3 lost 4 to 10 pounds. In all patients signs of heart failure, namely edema, congestion, and hepatomegaly, persisted and were improved only when digitalis and mersalyl were administered.

Beriberi Heart Disease, Response to Thiamine. Nine patients admitted to heavy drinking and 5 had eaten little food in the preceding 6 to 18 months. All were male, aged 24 to 48 years. No cases were seen in women although many African females drink heavily. A similar predominance among males has been noted in India.[2]

Nine patients had been ill for 1 to 3 weeks and one for 3 months. The usual complaints were swelling of the feet and breathlessness. Two gave a history suggestive of paroxysmal nocturnal dyspnea. All patients had signs of mild congestive cardiac failure. None looked ill or distressed and only 2 had a few crepitations over the lung bases. The venous engorgement was usually moderate (jugular venous pressure to the level of the hyoid with the patient sitting at 60°), the liver was enlarged 1 to 4 finger-breadths and was slightly tender. All patients had edema of the feet and sacrum; the face was affected in 5. They lost from 10 to 25 pounds in weight during their hospital stay.

Seven patients had no signs of polyneuritis, 1 had tender calves, and 2 absent knee and ankle jerks.

Nine patients had throbbing carotid pulses, hot hands and feet, water-hammer brachial pulses, and audible pistol-shot sounds over the femoral arteries. Only 1 patient had cool hands and full, rather than collapsing, pulses.

The blood pressure ranged from 110 to 170 systolic and 65 to 90 diastolic; the pulse pressure ranged from 45 to 80 and in 8 cases was 60 to 80 mm. Hg. The pulse rate ranged from 80 to 120. No heaves or thrusts were felt over the precordium; in 5 a mild tumbling sensation was appreciable. Slight cardiac enlargement to the left could be elicited by percussion in only 2 cases. Eight had a grade II late systolic murmur at the mitral area. The pulmonary second sound was usually loud and split. A protodiastolic third sound was heard in 4 cases.

Mild exercise usually accentuated the circulatory phenomena and uncovered a third heart sound. Carotid sinus pressure produced no striking effects on the pulse rate. In 4 with more florid signs, pitressin 1 ml. intramuscularly produced dramatic effects in a few minutes; it slowed the pulse, elevated the diastolic pressure, reduced the throbbing, and caused disappearance of the third heart sound. The effects usually wore off in 15 minutes and were sometimes followed by diuresis. Saccharin arm-to-tongue circulation times in 6 cases ranged between 10 and 20 seconds. The electrocardiogram usually showed tachycardia but no arrhythmias. Inversion of T waves, S-T deviations, and serial changes in the electrocardiogram were frequently seen but were probably not specific for beriberi.[3] The Q-T and P-R intervals were within normal limits.

None of the 10 patients suffered from anemia, nephritis, fever, thyrotoxicosis, or other conditions associated with a hyperkinetic circulation. No evidence of other vitamin deficiencies was noted. No acute pernicious cases (shosin) were seen.

The heart was moderately enlarged and of a fairly characteristic shape (fig. 2). The right border showed 2 curves, an upper one due to a dynamically expanded aorta (it usually disappeared with recovery), and a lower one due to right atrial or ventricular enlargement. The left border showed a prominent main pulmonary artery and a rounded and elongated left lower segment. The secondary branches of the pulmonary artery were never grossly distended. Three cases showed mild pul-

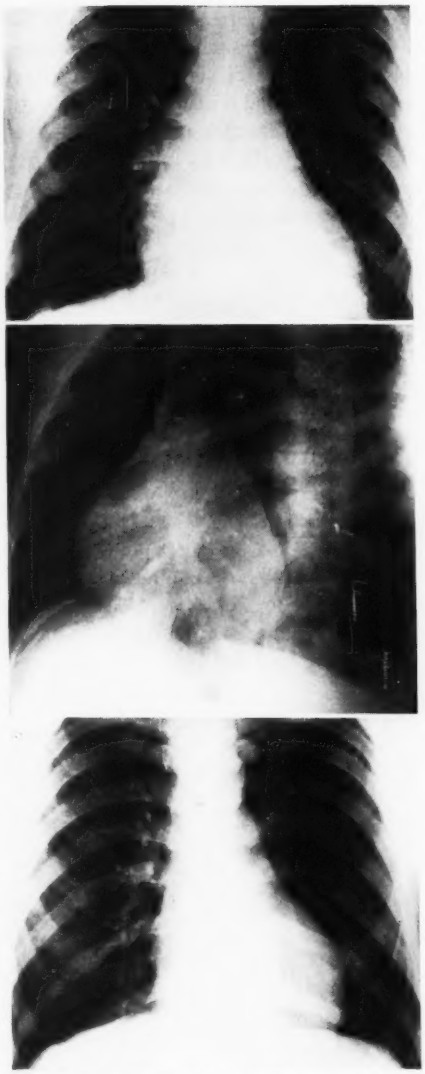


FIG. 2. *Top*. Beriberi heart disease. *Middle*. The oblique view shows enlargement of both ventricles. *Bottom*. The same patient 3 weeks later. One year later there was no change.

monary congestion; 2 had small pleural effusions. Radioscopy in 8 cases revealed active throbbing (so called "aortic" movement) of the ventricles, aorta, and main pulmonary artery. In the oblique views the ventricular enlargement appeared to involve both ventricles equally in 7 cases but mainly the right in the remaining 3. In 2 cases the contraction of the whole heart appeared much reduced probably because of the presence of a small pericardial effusion.

Response to Thiamine

Six of the 10 patients lost 0–3 pounds in 5 days on the low-thiamine diet and their physical signs remained unchanged. During this time the daily urinary output was usually low, but in some cases rose as high as 80 ounces in 24 hours, possibly because the patients were allowed to drink unrestricted amounts of water.

The diuresis (60–80 ozs.) occurred within 12 hours in 2 cases but was delayed for 24 hours in 4 others. In these 6 cases the physical signs and all the edema disappeared in 5 to 9 days; the pulse rate slowed to 50–60 per minute, the blood pressure remained at the same level or rose but the pulse lost its water-hammer quality. The heart size returned to normal within 3 weeks. Two cases developed a mild fever for a few days. Tenderness of the calves persisted in 2 cases for 6 weeks and reflexes when absent did not return.

Three patients showed an incomplete response on the low-thiamine diet. They lost most of their edema and systemic venous congestion over a period of 5 to 9 days but the tachycardia and the water-hammer pulse persisted. One patient started vomiting persistently, the second developed a fever and looked ill, and the third complained of extreme calf tenderness. The administration of thiamine at this stage dispersed these signs, except calf tenderness, in 2 or 3 days. It was possible that these patients may have lost their signs without any treatment and to test this point a fourth patient who had partially responded was given digitalis and mersalyl and kept on the low-thiamine diet. He lost all his edema but the water-hammer pulse and tachycardia persisted. On the fifth day he collapsed and became cold and sweaty. He was given intravenous thiamine and recovered in half an hour and lost his abnormal circulatory signs after a further 3 days of thiamine therapy.

Five cases have been followed for 6 to 15 months. One has relapsed but none has developed an enlarged heart.

Syndrome A

Cases of Heart Failure Unresponsive to Thiamine (*fig. 3*). All 3 cases were males aged 32 to 45 years and only 1 was an alcoholic. They had

been ill with edema and breathlessness for 1 to 21 days and 1 gave a history suggestive of paroxysmal nocturnal dyspnea.

They had moderately severe heart failure with normal blood pressures. There was no cyanosis, valvular defect, or indeed any obvious cause for the heart failure. Two had triple rhythm and 4 had crepitations over the lung bases. X-ray showed enlargement of the heart without, however, a characteristic shape. On radioscopy the heart contracted actively in 2 cases but appeared virtually immobile in the third. On the therapeutic regime 2 lost most of their edema after 10 days of thiamine; unlike cases of beriberi however, the elevated jugular venous pressure and hepatomegaly persisted and disappeared only after a further 2 weeks of bed rest. The third case showed no improvement at all until digitalis and mersalyl were administered. In all cases the heart size became normal in 4 weeks. All 3 have been followed for 9 to 15 months and none has shown recurrence of signs or increase in heart size.

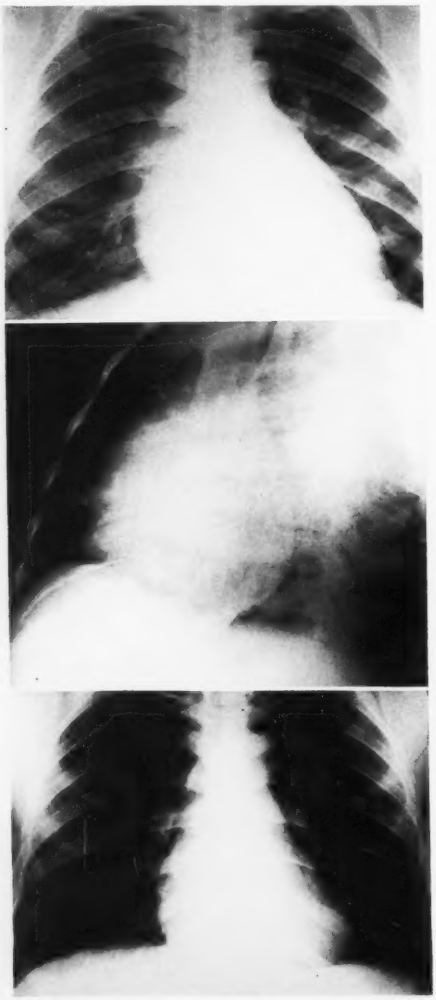


FIG. 3. *Top and middle.* Acute heart failure. Poor pulsation radioscopically. *Bottom.* Four weeks later. No response to low-thiamine diet or to thiamine. Response after 10 days of digitalis and mercurials. Twelve months later the x-ray appearances were unchanged (syndrome A).

Syndrome B

Heart Failure Responding Completely to the Low Thiamine Diet (*fig. 4*). All 3 patients were males aged 34 to 40 years and were heavy drinkers; they had been ill for 1 or 2 weeks with swelling of the legs and breathlessness. Clinically, these patients were indistinguishable

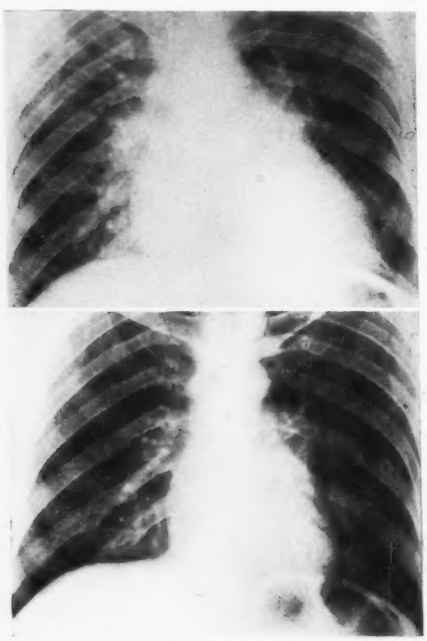


FIG. 4. *Top.* Acute heart failure. *Bottom.* Seventeen days later. Response on bed rest and low-thiamine diet (syndrome B). Fifteen months later there was no change.

from cases of beriberi heart failure. They were all in a state of mild congestive cardiac failure. They all had wide pulse pressures, soft mitral systolic murmurs, loud and split pulmonary second sounds, and 1 had a protodiastolic third sound as well. In 2, saccharin circulation times measured 11 and 15 seconds respectively. The electrocardiograms showed nonspecific changes. Pitressin tests in 2 were equivocal. X-ray revealed moderate enlargement of the heart but not a characteristic shape. (One had a long ventricular outflow tract, 1 had a boot shape, and the third resembled beriberi heart.) Only 1 had pulmonary congestion. Radioscopically the heart contracted actively in all 3 cases.

These patients differed from cases of beriberi in their immediate and complete response on the low-thiamine diet and bed rest. Within 24

TABLE 1.—*Laboratory Findings in Sixteen Cases of Acute Heart Failure and Eight Cases of Hunger Edema*

	Alkaline phosphatase (K.A. units)	Liver function tests				Serum cholesterol (mg. %)	Serum proteins			Hemoglobin (Gm. %)	Erythrocyte Sedimentation Rate (Wintrobe) (mm./1 hr.)
		TT	TF	CR	TA		Total	Albumin	Globulin		
Beriberi	3.7	3.5	3+	4+	3+	115	6.7	3.0	3.7	16.6	19
	14.0	5.5	3+	4+	3+	110	7.0	3.4	3.6	17.6	24
	8.5	4.5	4+	4+	3+	145	8.5	4.7	3.8	16.4	9
	4.4	3.5	0	1+	0	—	—	—	—	—	—
	6.0	—	—	—	—	140	6.7	3.6	3.1	15.6	3
	—	4.5	1+	4+	3+	200	6.6	3.4	3.2	16.3	18
	—	2.5	1+	3+	3+	110	6.6	3.4	3.2	15.0	—
	6.6	2.5	0	0	3+	145	6.5	2.2	4.3	13.8	—
	—	1.5	0	3+	0	—	7.1	3.6	3.5	15.8	2
	—	—	—	—	—	—	7.0	2.5	4.5	15.6	16
Mean						138	7.0	3.3	3.7		
Syndrome A	7.5	—	—	—	—	125	6.6	3.0	3.6	16.1	28
	—	—	—	—	—	140	7.5	4.1	3.4	16.0	—
	—	4.0	3+	4+	2+	170	7.0	3.3	3.7	15.6	31
Mean						145	7.0	3.5	3.6		
Syndrome B	—	4.5	1+	4+	3+	200	6.6	3.4	3.2	16.3	18
	—	—	—	—	—	—	7.3	3.5	3.8	17.4	3
	5.1	3.5	3+	3+	0	200	6.7	3.0	3.7	15.0	30
Mean						200	6.9	3.3	3.6		
Hunger edema	8.4	3.5	—	4+	1+	195	—	—	—	—	—
	7.2	1.5	0	1+	1+	165	7.7	3.6	4.1	17.9	17
	6.2	5.0	4+	4+	1+	120	7.4	3.7	3.7	18.0	2
	—	—	—	—	—	—	7.3	3.5	3.8	17.4	3
	5.8	3.5	4+	3+	0	—	7.4	3.3	4.1	14.4	3
	9.8	4.0	0	4+	3+	—	6.4	3.0	3.4	16.7	7
	10.0	3.5	0	3+	3+	—	6.2	2.5	3.7	13.0	—
	—	—	—	—	—	—	6.7	2.4	4.3	—	—
Mean						160	7.0	3.1	3.9		

TT = Thymol turbidity; TF = Thymol flocculation; CR = Colloidal red test; TA = Uckos' modification of the Takata-Ara test.

hours they started losing weight and passed large quantities of urine (94–120 ozs.). Within 6 to 8 days they had lost all their edema (12–25 lbs.) and physical signs. One patient who started losing weight was kept on a low-thiamine diet and was treated with digitalis and mersalyl as well; he recovered completely in 5 days. All 3 patients have been followed for periods up to 15 months and have shown no recurrence of symptoms or signs and no radiologic enlargement of the heart.

Edema without Cardiac Enlargement, 10 Cases. Two patients, both males, showed no improvement on the low-thiamine diet but when thiamine was added they recovered rapidly and completely, indicating that the edema was due to vitamin B_1 deficiency.

The remaining 8 cases of edema responded completely on the thiamine-low diet and bed rest. There was one female in this group. Their ages ranged from 30 to 50 years. Six were admitted alcoholics and 1 had been in jail for 18 months. All had developed swelling and breathlessness in the previous 3 to 21 days.

Four of these patients, 1 female and 3 males, in addition to their edema showed striking circulatory phenomena, namely moderately raised jugular venous pressure, tender hepatomegaly (1–3 fingerbreadths), hot extremities, water-hammer pulses, and tachycardia (80–120). On auscultation 3 had soft systolic mitral murmurs and 1 had triple rhythm. Circulation times in 3 measured 12, 13, and 17 seconds respectively. Pitressin tests were dramatically positive in 2. Clinically, they were indistinguishable from cases of beriberi heart failure or from syndrome B but differed from both these types in showing no radiologic enlargement of the heart. They resembled syndrome B, in their immediate and dramatic response while on a low-thiamine diet. All recovered in 3 to 7 days. No subsequent enlargement of the heart was observed in periods of 4 to 12 months.

Of the remaining 4 cases of edema none had clinically abnormal circulation. The pulse rate ranged from 65 to 90. On a low-thiamine diet all had a brisk and immediate diuresis and lost their edema (10–20 lbs.) in 5 to 7 days. In 2 the edema recurred in 2 and 6 weeks respectively.

No renal lesion was detected and there was no anemia. Liver function tests and blood proteins were abnormal but did not differ significantly from values found in the other groups (table 1).

Discussion

The first point to decide is whether the patients who responded on a low-thiamine diet were mild cases of beriberi responding to small quantities of vitamin B_1 in the diet. It must be pointed out that it was not found practical to maintain these African patients for any length of time on a lower vitamin B_1 intake, for such a diet was not bulky enough and made the subjects hungry and uncooperative. The diet used in this study supplied 0.25 to 0.3 mg. of vitamin B_1 in 24 hours and it has been estimated that an adult weighing 70 Kg. requires 0.65 to 1.25 mg. of vitamin B_1 per day to prevent the development of deficiency.[4] On the other hand, patients at rest in bed probably require less vitamin B_1 than more active people[5] and, moreover, it is possible that synthesis of vitamin B_1 may occur in subjects subsisting on a low-thiamine diet.[6] Although these Africans were maintained on a diet that theoretically could not cure beriberi, nevertheless this possibility cannot be entirely dismissed.

If these syndromes are not evidence of thiamine deficiency, what are they? Edema without cardiac enlargement or venous congestion is common among Africans. It is aggravated by exercise, reduced or dispersed by bed rest, and often recurs within a short time after the patient leaves the hospital. It is not due to heart failure or renal disease. It is commonly associated with abnormal liver function tests and a comparatively low albumin concentration in the serum—features however that are also found among outwardly healthy Africans and in many medical patients without edema.[7] From its clinical features it corresponds with the description of hunger edema, which occurred in undernourished Europeans after the last 2 great wars. The studies of McCance[8] and others have established that in hunger edema the extracellular space is expanded; McCance postulated that the excess fluid moves freely about the body and may invade the intravascular compartment to produce changes in

blood volume. There is already some evidence that scorbutic Africans suffering from edema show variations in blood volume as judged by elevation of jugular venous pressure and wide fluctuations in hemoglobin levels from day to day.[9] The clinical features of the patients with noncardiac edema and with certain of the heart failures (syndrome B) in this study are so similar as to suggest that they may represent gradations of the same underlying fault, namely hypervolemia. Maneuvers that increase the blood volume both in man and in animals are known to produce a hyperkinetic state and ultimately heart failure.[10]

The 3 cases of heart failure in syndrome A did not respond to thiamine, no obvious cause was apparent for the heart failure and radioscopy showed poor cardiac pulsation in 1 patient. In these features they resembled the early stage of nutritional heart disease described by Gillanders.[1] All have been at home for periods of 9 to 15 months and presumably have been living on their accustomed home diet. None have relapsed and in this respect they differ from Gillanders' group whose heart failure recurred within a short time after return to the deficient home diet. Whether these examples represent a homogeneous group of heart disease is not yet known.

Idiopathic cardiac hypertrophy is commonly found at postmortem examination among Africans in South Africa.[11] Both ventricles are hypertrophied, there is a tendency to mural thrombosis, and histology reveals no specific lesion. No obvious cause for the hypertrophy can be found. A similar type of cardiac hypertrophy has been described among West Africans.[12] In East Africans cardiac hypertrophy is commonly associated with extensive endocardial fibrosis,[13] probably due to massive organization of mural thrombi. In Johannesburg, Becker's group[14] have described a heterogeneous group of heart failures, some of which are probably examples of idiopathic cardiac hypertrophy studied by special histochemical methods.

In the Bantu, Gillanders[1] and Higginson[11] studied the etiology of the condition and excluded such factors as glycogen-storage disease and deficiency of vitamins B_1 and E. At an early stage of the disease Gillanders was able to reverse the cardiomegaly by feeding the patient an adequate diet, and he could reproduce the heart failure by returning the patient to his deficient home diet. Many of his patients suffered from liver disease. For these reasons he concluded that the condition was due to malnutrition. Liver disease, however, is commonly found in the Bantu and in many who do not have idiopathic cardiac hypertrophy; idiopathic cardiac hypertrophy is found in young children who have not suffered from malnutrition[15] and certainly many adults with idiopathic cardiac hypertrophy do not show the stigmata of malnutrition in the accepted sense.

Idiopathic cardiac hypertrophy is found throughout Africa. As far as can be ascertained, the condition has not been reported in other undernourished communities in the Far East and India. Although the mechanism is not understood, it seems reasonable to assume that the condition is in some way due to malnutrition, possibly to a particular dietetic pattern.

One of the basic problems about the disease is why both right and left ventricles should hypertrophy in the absence of pulmonary or systemic hypertension or valvular defects. Can it be due to chronic vitamin B_1 deficiency or to repeated attacks of cardiac dilatation associated with hypervolemia?

It has been suggested that vitamin B_1 deficiency may be a cause of cardiac hypertrophy. This hypothesis was first advanced by Weiss[16-18] who found examples of unresponsive heart failure associated with cardiac hypertrophy among a group of undernourished subjects who were probably suffering from vitamin B_1 deficiency as well. The idea has been supported by others.[19-21] The evidence is by no means conclusive and has been challenged by Wintrobe,[22] who doubts whether chronic heart failure can ever be attributed to vitamin B_1 deficiency. It is not known whether cardiac hypertrophy is common in the Far East or in India, where beriberi is endemic. On the contrary, there is evidence that prisoners of war who suffered from cardiac beriberi in Japan have not developed chronic heart disease.[23] The evidence from these Africans also lends support to the view that the acute form of beriberi does not

lead to chronic heart disease. Nevertheless, the possibility exists that subacute (subclinical) deficiency may be a cause of cardiac hypertrophy although this has not been demonstrated in animals.[24, 25] As far as Africans are concerned, it is not known whether beriberi is an endemic disease or whether it is confined to urban natives who live in poor economic circumstances and drink alcohol to excess. Judging by food surveys[26] of urban and rural Africans, it would seem that they obtain adequate quantities of vitamin B_1 in their diet. Although hunger edema is commonly seen in this hospital, the same doubt exists whether it is a disease indigenous to Africans or only occurs in urban areas and thus whether it could be reasonably considered a factor in the production of idiopathic cardiac hypertrophy.

Summary

Sixteen cases of acute reversible heart failure in Africans have been studied. They have been arbitrarily classified into 3 groups on the basis of their response to a low-thiamine diet and to injections of thiamine. Only 10 cases were examples of vitamin B_1 deficiency (beriberi heart disease).

Eight cases of nutritional edema without cardiac enlargement were studied in the same way. Four of these patients and 1 group of heart failures had similar clinical features and responded on a low-thiamine diet. It is suggested that these similarities were due to the same basic abnormality, hypervolemia.

The role of vitamin B_1 deficiency and nutritional edema in idiopathic cardiac hypertrophy of the Bantu is briefly discussed.

Acknowledgment

I would like to thank Dr. A. W. Lategan, Director of the National Nutrition Research Institute, for the determinations of thiamine in the diet; Miss H. C. Pledger, M.S., Senior Dietician, Baragwanath Hospital, for planning and preparing the diets; Miss A. C. Dick, B.Sc., Senior Librarian Medical School, for her helpful assistance, and many colleagues at Baragwanath Hospital for their cooperation and assistance. The expenses of this investigation were defrayed by a grant from the South African Council for Scientific and Industrial Research.

Summario in Interlingua

Esseva studiate 16 casos de acute reversibile disfallimento cardiac in africanos. Super le base del responsas a dietas de basse contento de thiamina e a injectiones de thiamina, le casos esseva classificate arbitrarimente in 3 gruppos. Solmente 10 del casos esseva exemplos de carentia de vitamina B_1 (morbo cardiac beriberi).

Octo casos de edema nutritional sin allargamento cardiac esseva studiate in le mesme maniera. Quatro de iste patientes e un del gruppos de casos de disfallimento cardiac habeva simile aspectos clinic e respondeva a dietas a basse contento de thiamina. Es suggerite que iste similitudes esseva le resultato de un identic anormalitate fundamental: hypervolemia.

Es presentate un breve discussion del rolo de carentia de vitamina B_1 e de edema nutritional in idiopathic hypertrophia cardiac in le bantu.

REFERENCES

1 Gillanders, A. D.: Nutritional heart disease. Brit. Heart. J. **13:** 177, 1951.

2 Yang, C. S., and Huang, K. K.: Beri-beri in Nanking. Chinese M. J. **48:** 20, 1934.

3 Grusin, H.: Peculiarities of the Africans' electrocardiogram and the changes observed in serial studies. Circulation **9:** 860, 1954.

4 Bicknell, F., and Prescott, F.: The Vitamins in Medicine. London, Heinemann, Ed. 2. 1947.

5 —, —: The Vitamins in Medicine. London, Heinemann, Ed. 3, 1953.

6 Najjar, V. A., and Holt, L. E.: The biosynthesis of thiamine in man and its implications in human nutrition. J. A. M. A. **123:** 683, 1943.

7 Bersohn, I., Wayburne, S., Hirsch, H., and Sussman, C. D.: A comparison of the serum protein, liver function tests and serological tests for syphilis in new-born African and European infants and their mothers. South African J. Clin. Sc. **5:** 35, 1954.

8 McCance, R. A.: Studies of undernutrition. Wuppertal. 1946–9 M. Res. Council, Special Report No: 275, 1951.

9 Grusin, H., and Kincaid-Smith, P. S.: Scurvy in adult Africans. Am. J. Clin. Nutrition **2:** 323, 1954.

10 Huckabee, W., Casten, G., and Harrison, T. R.: Experimental hypervolemic heart failure. Its bearing on certain general principles of heart failure. Circulation **1:** 343, 1950.

11 Higginson, J. S., Gillanders, A. D., and

MURRAY, J. F.: Heart in chronic malnutrition. Brit. Heart. J. **14:** 213, 1952.

[12] BEDFORD, D. E., AND KONSTAM, G. L. S.: Heart failure of unknown etiology in Africans. Brit. Heart. J. **8:** 236, 1946.

[13] BALL, J. D., WILLIAMS, A. W., AND DAVIES, J. N. P.: Endomyocardial fibrosis. Lancet **1:** 1049, 1954.

[14] BECKER, B. J. P., CHATGIDAKIS, C. B., AND VAN LINGEN, B.: Cardiovascular collagenosis with parietal endocardial thrombosis; clinicopathologic study of 40 cases. Circulation **7:** 345, 1953.

[15] ALTMAN, H., AND STEIN, H.: Idiopathic hypertrophy of the heart in African children: A report of 4 cases. Brit. M. J. **1:** 1207, 1956.

[16] WEISS, S., AND WILKINS, R. W.: Nature of the cardiovascular disturbances in nutritional deficiency states. (Beri-beri). Ann. Int. Med. **11:** 104, 1938.

[17] —, AND —: Disturbance of the cardiovascular system in nutritional deficiency. J. A. M. A. **109:** 786, 1937.

[18] —: Occidental beri-beri with cardiovascular manifestations. Its relation to thiamine deficiency. J. A. M. A. **115:** 832, 1940.

[19] GOODHART, R., AND JOLLIFFE, N.: The role of nutritional deficiencies in the production of cardiovascular disturbances in the alcohol addict. Am. Heart J. **15:** 568, 1938.

[20] DOCK, W.: Marked cardiac hypertrophy and mural thrombosis in ventricles in beri-beri heart. Tr. A. Am. Physicians **55:** 61, 1940.

[21] SMITH, J. J., AND FURTH, J.: Fibrosis of the endocardium and the myocardium with mural thrombosis. Notes on its relation to isolated (Fiedler's) myocarditis and to beri-beri heart. Arch. Int. Med. **71:** 602, 1948.

[22] WINTROBE, M. M.: Relation of nutritional deficiency to cardiac dysfunction. Arch. Int. Med. **176:** 341, 1945.

[23] GRIFFITH, R. L.: Condition of the heart following beriberi and malnutrition. Arch. Int. Med. **89:** 743, 1952.

[24] SWANK, R. L.: Avian thiamine deficiency; correlation of pathology and clinical behaviour. J. Exper. Med. **71:** 683, 1940.

[25] DE SOLDATI, L.: Los trastornos circulatorios del perro en avitaminosis B.1.; el pulso, la tension arterial y el electrocardiograma. Rev. Soc. argent. de biol. **15:** 428, 1939.

[26] WALKER, A. R. P.: Personal communication. 1956.

Withering's prominence as a botanist is sometimes lost sight of because of his discovery of digitalis. His years at Stafford had culminated in the publication of a two-volume work entitled *Botanical Arrangement of Vegetables* (1776), which earned him the title of the English Linnaeus. On the Continent he was probably better known for his botany than he was for the introduction of digitalis.

Withering also achieved an eminent position as a mineralogist principally for his discovery of barium carbonate which is still known as "Witherite" in honor of the man who first proved its chemical constitution, it having been so named by the great German geologist, Werner.—JOHN F. FULTON.—*The Place of William Withering in Scientific Medicine.* J. Hist. of Med. & Allied Sc., **8:** 14, 1953.

Design of an Ultra Low Frequency Force Ballistocardiograph on the Principle of the Horizontal Pendulum

By T. J. Reeves, M. D., W. B. Jones, M.D., and L. L. Hefner, M.D.

A low frequency ballistocardiographic system based on the principle of the horizontal pendulum is described. By increasing the coupling of the body to the bed and by the use of an extended frequency range accelerometer, ballistocardiograms having clearly defined high frequency components were recorded. The physical principles of such a system are briefly reviewed.

THE classic studies of Starr and associates,[1] demonstrating that the *displacement* of a high frequency ballistocardiograph is related to the acceleration of cardiac ejection, opened a new and important field of physiology. The unique information so gained is perhaps more closely related to the functional status of the myocardium than any other accessible measurement. Recent analyses by von Rittern,[2] Burger and co-workers,[3] and Talbot and Harrison,[4–6] have shown that the *acceleration* of ultra low frequency or aperiodic ballistocardiographs may yield the same information over a wider frequency range and with less distortion due to the resonant properties of the body. Using the basic concepts outlined in these studies, we have devised a system that records high frequency force components not visible in previously published tracings. These high frequency components have definite physiologic significance of fundamental importance as will be presented in a subsequent communication. The purpose of this paper is to describe the system used to obtain the extended frequency response necessary to record these components, and to present its physical validation. In addition, typical records are presented.

The factors to be considered in the design of a low-frequency ballistocardiograph include the following:

1. The natural frequency of the system, which must be significantly lower than the frequencies of the forces to be measured.
2. The damping of the system that can influence both the lower and the upper frequency ranges.
3. The relative motion between the body and the bed. This factor is of the utmost importance in determining the recording fidelity of the instrument in the upper range of frequencies.
4. The resonant characteristics of the ballistocardiograph. There should be no tendency of the ballistocardiograph or any of its components to resonate within the range of frequencies of the applied forces.
5. The motion should be sensed by an instrument that can give an undistorted record of acceleration throughout the entire spectrum of forcing frequencies.

Method

A seismographic suspension* (i.e., a horizontal pendulum) was adapted to ballistocardiography so that the above requirements were met (figs. 1 and 2). This ballistocardiograph consists of a light platform suspended from a wall by light cables but pushed away from the wall by an arm on a ball-socket joint. The suspension is such as to create a nearly horizontal pendulum having a very long period. The platform is an aluminum honeycomb† panel trimmed to the general contour of the body for the sake of lightness. Its weight so trimmed is 8 pounds. The cables are $\frac{3}{64}$-inch stainless steel. The cables are attached below to the supporting V arm, which is

From the Department of Medicine, Medical College of Alabama and the Medical Service of the Veterans Administration Hospital, Birmingham, Ala.

Aided by grants from the Life Insurance Medical Research Fund, the Ingco Foundation, and the U. S. Public Health Service.

Drs. Jones and Hefner are Trainees of the National Heart Institute, National Institutes of Health of the U. S. Public Health Service.

* Dr. Bert Boone and Mr. Frank Noble of the National Institutes of Health originally suggested this suspension, and participated in the initial design. Their help is gratefully acknowledged.

† Available from the Honeycomb Corporation of America, Bridgeport, Conn.

FIG. 1. Photograph of the ballistocardiograph. The straps shown on the platform are fastened around the patient's shoulders, thereby fixing him firmly to the footboard. The accelerometer, not shown in the picture, is mounted under the front edge of the platform in the center.

of 1-inch aluminum alloy tubing. These cables are suspended by a double ring hinge that projects 2 inches farther from the wall than the lower joint.

This forward displacement of the upper bearing is so designed in order to allow slow periodic motion of the bed. If the 2 bearings were exactly vertical the bed would be aperiodic. However, since such a state would be extremely difficult to maintain, the periodicity is desirable for the sake of stability.

The length of the supporting tubing, which is the pendulum arm, has 2 important effects. The period of a horizontal pendulum is determined by the angle between a vertical line and a line connecting the upper and the lower hinges and by the horizontal length of the pendulum arm. By adjusting either or both of these factors, the period of the pendulum may be controlled at will, including theoretic aperiodicity. The relationship of the factors is expressed by the formula:

$$f = \frac{1}{2\pi}\sqrt{\frac{g \sin\theta}{l}}$$

where θ is the angle from the vertical of a line between the 2 hinges, g is the acceleration due to gravity, and l is the length of the horizontal pendulum arm. The second major consideration in the length of the pendulum arm is the effect of the circular motion of the pendulum upon the transmission of the linear force. The actual motion imparted to the bed by the circulatory force is so small compared to the radius employed (30 inches) as to render the distortion negligible.

The natural frequency of the bed should be significantly below the lowest frequencies of force encountered. At a degree of damping considerably higher than that present in this system, Burger found a natural frequency of 0.3 cycle per second entirely adequate. The frequency of this bed as described is 0.1 c.p.s., with a damping factor of 0.026. The lower end of the undistorted frequency response range of this physical system would then be less than 0.5 c.p.s. For further details on this aspect of the problem the analysis of Burger should be consulted.[3]

Relative Motion of Body and Bed. In 1953 von Wittern described his ballistocardiographic system, including a discussion of the factors affecting the frequency response range of any low frequency ballistocardiograph.[2] He defined 2 frequencies, f_1 and f_2, between which acceleration recorded from the bed is proportional to the circulatory forces. Similarly, for ballistocardiographic frequencies between f_1 and f_2, velocity from the bed is proportional to the momentum of the circulatory mass, and displacement of the bed is proportional to the mass displacement of the circulatory mass. (These assertions ignore whatever distortion occurs in transmission through the internal body network.) Therefore, f_1 should be lower than the lowest forcing frequencies to be measured, and f_2 higher than the highest forcing frequencies to be measured. Otherwise, the record would be distorted in amplitude and time.

The f_1 frequency is very close to the natural frequency of the loaded bed. This frequency may be set at any desired level in a horizontal pendulum, and, therefore, is no problem at all. The present bed has a natural frequency of 0.1 c.p.s., loaded or unloaded.

The f_2 frequency is the frequency of relative motion between the body and the bed. The frequency of any vibratory system depends upon 2 factors—the mass that is oscillating and the strength of the spring involved, according to the relation:

$$f = \frac{1}{2\pi}\sqrt{\frac{k}{m}} \qquad (1)$$

where f = frequency, k = spring constant, m = mass involved. If the subject lies on a fixed platform:

$$f_b = \frac{1}{2\pi}\sqrt{\frac{k_b}{m_b}} \qquad (2)$$

where f_b = natural frequency of body on a fixed platform, k_b = spring constant of body, m_b = mass of body.

The f_b frequency has been found to be about 4 or 5 c.p.s. on a fixed platform when no footboard or shoulder straps are used. If, however, both shoulder straps and footboard are used, k_b is quadrupled,

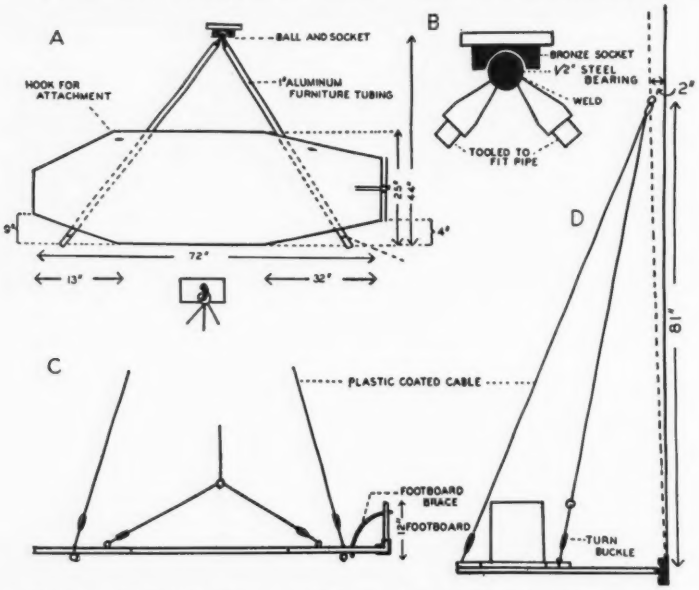


FIG. 2. *A*. Top view. *B*. Detail of bearing. *C*. Front view. *D*. Side view. The panel of honeycomb material is of Alclad aluminum plates, 0.012-inch with $\frac{3}{8}$-inch hexagonal honeycomb, over-all thickness 1 inch. The support is 1-inch by .049-inch aluminum alloy tubing and the cable is $\frac{3}{64}$-inch stainless steel. The ball is a $\frac{1}{2}$-inch steel bearing welded to a steel V tip for insertion into the tubing. The socket is drilled bronze. The footboard brace is of $\frac{1}{8}$-inch aluminum rod. The cables are attached above to a steel ring that is interlocked with an eyebolt attached to the wall. The total cost of the material is approximately $80.00.

approximately, so that f_b is raised to about 9 c.p.s. If the body lies on a light freely movable platform instead of on a fixed platform, the physical situation exists in which a large mass (the subject) is connected to a small mass (the bed) by a spring (the body tissues). If the 2 masses vibrate relative to one another, as an approximation the large mass may be assumed to be fixed, with the small mass vibrating upon it through the connecting spring.

Mathematically:

$$f_2 = \frac{1}{2\pi}\sqrt{\frac{k_b}{m_t}} \qquad (3)$$

where f_2 = frequency of relative motion between the 2 masses, k_b = spring constant of body, m_t = mass of bed.

The spring constant, k_b which is difficult to determine directly, may be eliminated from the above equation by dividing equation 3 by equation 2 and simplifying:

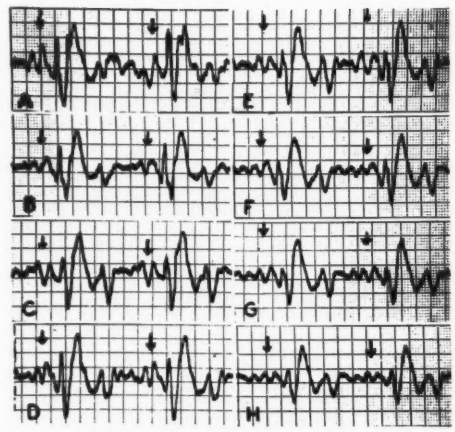
$$\frac{f_2}{f_b} = \frac{\frac{1}{2\pi}\sqrt{\frac{k_b}{m_t}}}{\frac{1}{2\pi}\sqrt{\frac{k_b}{m_b}}} \text{ or } f_2 = f_b\sqrt{\frac{m_b}{m_t}} \qquad (4)$$

The above derivation is essentially the same as that of von Wittern, but arranged so as to show that f_2 is the frequency of relative motion between the body and the bed. The formula shows that for f_2 to be as high as possible: (a) f_b should be as high as possible (i.e., footboards and shoulder straps should be used); and (b) the mass of the bed should be as small as possible. The horizontal pendulum bed being described is provided with a footboard and shoulder straps. The total weight of the bed is 12 pounds. The f_2 then, for a 192 pound man, could be calculated:

$$f_2 = 9\sqrt{\frac{192}{12}} = 36 \text{ c.p.s.}$$

The upper limit of frequency fidelity on our system would range then from about 30 c.p.s. for a 120-pound subject to over 40 c.p.s. for a heavy subject.

It would, of course, be preferable to determine f_2 experimentally, rather than to rely on mathematical calculations. We have attempted an experiment for determination of f_2 on several subjects, but have encountered difficulties such that the results cannot be presented with complete confidence. If the ballistocardiographic system loaded with a subject is oscillated with steadily increasing frequency, and velocity or force recorded as the frequency of the forcing oscillation approaches the f_2 point, a "node"



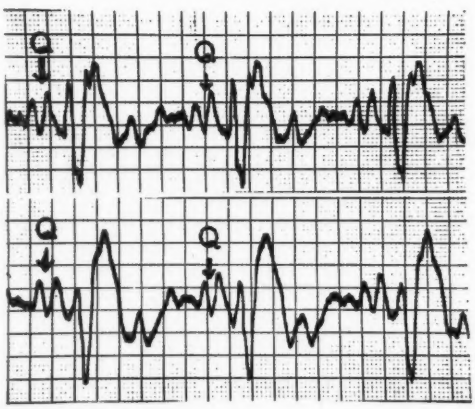


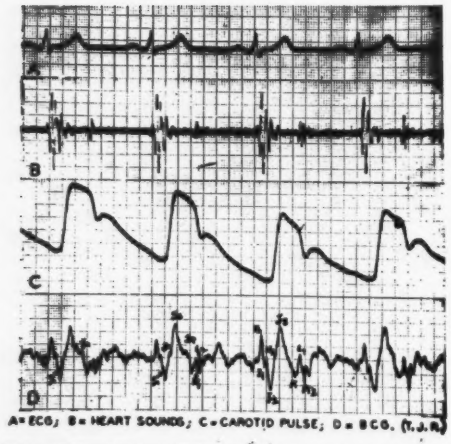
FIG. 3 *Top.* A series of force ballistocardiograms made on a patient with mitral stenosis. The f_2 point (the frequency of relative motion between the body and bed) has been progressively lowered to demonstrate the distortions in amplitude, time, and contour that result when the f_2 point is low enough to be within the frequency range of ballistocardiographic interest. (The f_2 point may be lowered by omitting shoulder straps, or footboard, or both, and by adding sandbags to the ballistocardiographic bed). In *A*, the calculated f_2 was 30 c.p.s. In *B* through *H*, the calculated f_2 points are approximately 23, 17, 13, 10, 8, 7, and 6 c.p.s, respectively. Note the progressive disappearance or distortion of some of the distinctive high frequency features of *A*. The arrows represent the onset of the QRS complexes.

FIG. 4 *Bottom.* Ballistocardiograms from a young woman 2 weeks after mitral commissurotomy. The simultaneously recorded ballistocardiograms above exhibit marked difference in relative amplitude of some of the deflections, as well as significant phase shift. The lower record was made by a commercially available accelerometer having a sharp roll-off of the frequency response at 17 c.p.s. The top tracing was from the mercury capillary accelerometer. Note especially the G-H amplitude, the clear separation of 2 J peaks, and the notching of the H-I downstroke in the top tracing. None of these details are present in the lower record. Preliminary observations have indicated physiologic significance of such high frequency forces.

should appear—that is, the recorded amplitude should sharply increase, followed by a "roll-off" as the forcing frequency exceeds f_2 .This procedure has been carried out with a variety of mechanical oscillators applied to the ballistocardiographic system in various ways. With the use of the mercury capillary accelerometer and a heavy subject with a calculated f_2 over 40 c.p.s., no node and no roll-off were found at forcing frequencies rising from 5 to 40 c.p.s. With lighter subjects a node was invariably found quite close to the calculated f_2, but other nodes were also present at lower frequencies, so that no one node could be singled out as indubitably the f_2 point. It was found that the node thought to represent the f_2 point behaved as predicted with varying body weights, bed weights, and presence and absence of shoulder blocks or footboards. It was therefore considered that f_2 had been experimentally determined and found to agree with the calculated f_2, but the presence of one or more unexpected nodes at lower frequencies made certainty impossible. The presence of these nodes (which were actually of small magnitude) is important in itself. These nodes may well represent resonant frequencies of various parts of the body, such as the head or arms, vibrating independently of the body as a whole. Such a phenomenon has been considered by Talbot and Harrison[6] previously. These nodes demonstrate that at certain forcing frequencies the recorded ballistocardiographic waves will be subject to a certain amount of distortion, which is at present unavoidable. No one has been able to devise a method to force the body to vibrate as a unit at all frequencies of ballistocardiographic interest.

The vast differences in the contour of the ballistocardiographic waves with varying f_2 points is demonstrated by figure 3. The f_2 frequency may be gradually lowered on the same subject by removing shoulder blocks, footboards, and then by progressively increasing the mass of the bed. The progressive distortion of the force patterns results from loss of high frequency components and resonance of certain waves at various f_2 points. Thus we are able to duplicate the tracings of other force ballistocardiographs by deliberately reducing the frequency fidelity of this system.

Resonance of System. Distortion of the acceleration tracings in the above system can be produced by resonances of the ballistocardiographic table or of its supports, if these resonance points are within the ballistocardiographic frequency spectrum. That is,



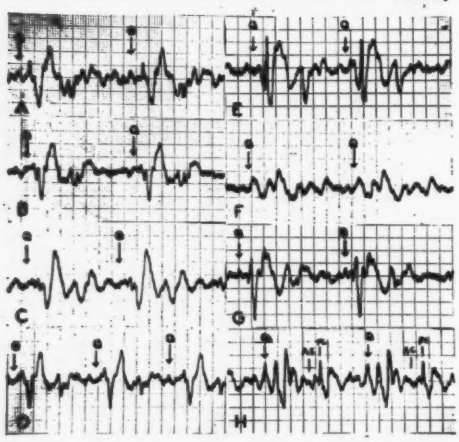


FIG. 5 *Top*. Simultaneously recorded electrocardiogram, carotid pulse, heart sounds, and ballistocardiogram from a normal subject. The last 2 cardiac cycles during an expiration and the first 2 of the succeeding inspiration are shown. Notice the high frequency wave forms, the reproducibility, and the respiratory variations of the ballistocardiographic waves, some of which have been labeled. It is apparent that standard nomenclature is overtaxed by the multiplicity of the high frequency ballistocardiographic waves.

FIG. 6 *Bottom*. *A*, *B*, *C*, and *D*, normal subjects. Note the consistency of the pattern. *E* was taken on a patient with mitral stenosis; *F* on a patient with an old posterior infarction and congestive failure; *G* on a patient with aortic insufficiency and *H* on a patient with a ventricular septal defect. Note the low amplitude in *F*, although a fundamental pattern can be recognized. In *H*, it is of particular interest to note the large amplitude of the footward deflection at the time of the second component of the second heart sound. On this patient the delayed second component is synchronous with the delayed closure of the pulmonic valve. In tracing *H*, aortic closure (*AC*) and pulmonic closure (*PC*) have been marked. These times were obtained from simultaneously recorded carotid pulses and heart sounds.

if a force of varying frequency is applied to the bed, nodes are produced at the frequencies of natural resonances within the system. These resonances will amplify and distort in time any force having a similar frequency. Since any metal surface and any supporting wire has a resonant frequency, there will invariably be ballistocardiographic distortions at these frequencies. In the proposed system, this difficulty available accelerometer having a sharp roll-off of the has been minimized by using a plate of aluminum sandwich construction that has a natural frequency of about 50 c.p.s., which is above the frequency of relative motion, as is the natural frequency of the supporting wires with the tension of the body on the table. This has been demonstrated experimentally by placing a variable frequency resonator on the ballistocardiographic bed and recording at rates up to 50 c.p.s. Below this point the amplitude varies directly with force, illustrating the absence of significant distortion due to resonance of the system.

Transducer. For adequate registration of the acceleration ballistocardiograph a pickup is needed that is quantitatively accurate through the frequencies of the ballistocardiographic spectrum, without distortion of either high frequency or low frequency impulses. A satisfactory accelerometer for this system is the electrokinetic device described by Elliott and co-workers.[7] It consists of a capillary tube with alternate cells of mercury and sulfuric acid generating an electric current proportional to acceleration by the changing shape of the interfaces. This unit has been found to be easy to construct, sensitive beyond requirement, and free from distortion. Various commercial accelerometers tested in this laboratory have been found to be less satisfactory. One should bear in mind that the upper limit of frequency response of a commercial accelerometer as given by the manufacturers applies only to sinusoidal forces, and not necessarily to the transient forces encountered in ballistocardiography. The desirable properties of the mercury accelerometer include a flat frequency response far beyond ballistocardiographic requirements, absence of phase shift, a satisfactory output, adequate stability, and simplicity. The importance of an adequate accelerometer can be seen in figure 4, in which tracings on the same subject are compared, showing a tracing using the mercury accelerometer and another accelerometer with an upper frequency response of 17 c.p.s. As can be seen, high frequency components are not registered by the commercial accelerometer, which rolls off at 17 c.p.s. There is also an appreciable phase shift.

In construction of the accelerometer, it has been found that if the output amplitude is sufficiently

high, distortion from electric interference is minimized.*

Results

The force ballistocardiograms obtained by this system have the general configuration of records published from other ultra low frequency systems except for the presence of additional high frequency forces. The records have demonstrated a very consistent pattern in young normal subjects. An example of such a ballistocardiogram is shown in figure 5. The labeled points have been present in all normal subjects thus far studied.

Many of these points are of relatively high frequency and will not be seen in clarity if the frequency response of the system is appreciably less than the one described. The importance of this factor is clearly illustrated in figure 3.

The ballistocardiograms of various subjects with cardiovascular abnormality have been of great interest. In general it would appear that many aberrations in cardiovascular physiology are manifested by forces of high frequency. Although experience to date is too limited for any conclusion as to the significance of such high frequency phenomena, it would appear obvious that in the present state of ballistocardiography it is desirable to record all forces in their true proportion. A few examples of abnormal contrasted to normal ballistocardiograms are shown in figure 6.

Discussion

The upper range of linear response of any ballistocardiographic system is limited by the frequency of relative motion between the body and the bed. As previously mentioned, this frequency is a function of the elastic coupling of the body to the bed, the mass of the body, and the mass of the bed. This frequency can be raised by either lowering the mass of the bed or increasing the effective elastic springs of the body. The latter can be accomplished by footboards and by shoulder blocks or shoulder straps. The latter approach has been emphasized in this ballistocardiograph because of the engineering difficulties, especially resonances, encountered with the ultra light platforms. Published tracings from ultra light systems having a theoretically wide frequency response have failed to show the high frequency components that have been present with the system here reported. Some reasons for these differences may be the increased coupling obtained by the application of tight shoulder straps and the accelerometer with a satisfactory frequency response used in this study.

The significance of the increased frequency response range of this instrument depends upon the importance of cardiovascular forces of the higher frequency range. Data thus far obtained by such a technic have led to a conviction that highly significant forces in certain abnormal states will be found in the frequency range of 20 to 35 c.p.s. When the frequency response of the ballistocardiograph is deliberately lowered to 20 c.p.s., marked "normalization" of grossly abnormal patterns has been repeatedly observed (fig. 3). It is evident that exaggeration of any force by resonance within the ballistocardiographic spectrum will lead inevitably to inaccuracy of interpretation of such a force. The various possibilities considered here, including the relative frequency of the body and bed, the suspension, and the bed itself, have all been shown experimentally to be capable of marked distortion of the ballistocardiogram. Two factors inherent in this and other ballistocardiographic systems that may be responsible for distortion of amplitude or phase should be borne in mind. The first is the possible accentuation of recorded ballistocardiographic forces due to resonance near the frequency of relative motion between the body and the bed (the f_2 point). The second factor is the possible distortion of recorded ballistocardiographic forces due to the effects of the internal elastic suspension of the heart and blood vessels. The authors are aware of the possibility that some high frequency forces may have been exaggerated by

* The addition of a capacitor across the leads from the accelerometer has been found necessary to correct for the relatively short time constant of the instrument. The amount of capacitance varies slightly with each accelerometer but has been found to average .02 mfd. With the use of the proper capacitor, the accelerometer has been demonstrated to remain 180° out of phase with displacement through the frequencies tested, 1 to 35 c.p.s. Each accelerometer must be checked for phase and amplitude prior to use.

the presently described system because of the high f_2 point, but consider this unlikely on the basis of the oscillation experiment in which the amplitude of the node at the f_2 point was small. This indicates that there is little amplitude distortion at this point. Further, even granting a certain exaggeration of the high frequency ballistocardiographic components, it seems better to have these forces visible than almost completely absent, since they are believed to have physiologic and pathologic significance.[8] The other factor, the effect of the internal body elastic network, remains unknown.

Summary

Some of the considerations involved in the design of a low frequency undamped ballistocardiographic system have been discussed. A practical ballistocardiographic system based on the principle of the horizontal pendulum is described. By increasing the coupling of the body to the bed and using an accelerometer of extended frequency range, ballistocardiograms having force components of high frequency have been recorded. These forces have not been clearly shown in any previously published study, but appear to have physiologic significance.

Summario in Interlingua

Es discutite certe consideratione que interessa le construction de un non-tamponate ballistocardiographo a basse frequentia. Un practic systema ballistocardiographic, basate super le principio del pendulo horizontal, es describite. Per augmentar le accopulamento del corpore al lecto e per usar un accelerometro de un plus extense gamma de frequentias, ballistocardiogrammas esseva registrate que ha componentes de fortia de alte frequentia non clarmente monstrate in ulle previemente publicate studio sed nonobstante de apparente signification physiologic.

References

[1] Starr, I., Horwitz, D., Mayock, R. L., and Krumbhaar, E. B.: Standardization of the ballistocardiogram by stimulation of the heart's function at necropsy; with a clinical method for the estimation of cardiac strength and normal standards for it. Circulation **1:** 1073, 1950.

[2] Von Wittern, W.: Ballistocardiography with elimination of the influence of the vibration properties of the body. Am. Heart J. **46:** 705, 1953.

[3] Burger, H. C., Noordergraaf, A., and Verhagen, A. M. W.: Physical basis of the low frequency ballistocardiograph. Am. Heart J. **46:** 71, 1953.

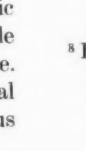
[4] Talbot, S. A., and Harrison, W. K., Jr.: Dynamic comparison of current ballistocardiographic methods. I. Artifacts in the dynamically simple ballistocardiographic methods. Circulation **12:** 577, 1955.

[5] —, and —: Dynamic comparison of current ballistocardiographic methods. II. Effect of a platform in ballistocardiographic dynamics. Circulation **12:** 845, 1955.

[6] —, and —: Dynamic comparison of current ballistocardiographic methods. III. Derivation of cardiovascular forces from body motions. Circulation **12:** 1022, 1955.

[7] Elliott, R. V., Packard, R. G., and Kyrazis, D. J.: Accelerations ballistocardiography. Design, construction, and application of a new instrument. Circulation **9:** 281, 1954.

[8] Reeves, T. J., Hefner, L. L., Jones, W. B., and Sparks, J. E.: Wide frequency range force ballistocardiogram: Its correlation with cardiovascular dynamics. Circulation **16:** 43, 1957.



To fight out a war, you must believe something and want something with all your might. So must you do to carry anything else to an end worth reaching. More than that, you must be willing to commit yourself to a course, perhaps a long and hard one, without being able to foresee exactly where you will come out.—O. W. Holmes, Jr., 1884.

Wide Frequency Range Force Ballistocardiogram

Its Correlation with Cardiovascular Dynamics

By T. J. Reeves, M.D., L. L. Hefner, M.D., W. B. Jones, M.D., and J. E. Sparks, M.D.

The ballistocardiograms of young normal subjects as recorded with a wide frequency range technic are described. These records contain high frequency forces not previously described. An analysis of these components in terms of known cardiovascular events strongly suggests that they have definite dynamic significance. In addition, these correlations offer evidence as to the genesis of some forces in the ballistocardiogram.

FORCE ballistocardiograms from a number of different laboratories, utilizing very low frequency or aperiodic systems, have been described and are strikingly similar one to the other.[1–3] The records are basically the same as those made from damped high frequency systems recorded as displacement[4] and also from undamped direct body displacement when the oscillations induced by the external tissues of the body are electronically cancelled.[5] The similarity of the force ballistocardiograms from such varied systems strongly supports the validity of the fundamental principles involved and heralds the end of an era of technical confusion and controversy.

Force ballistocardiograms recorded from this laboratory using a low frequency system of extended frequency range[6] have been observed to differ markedly in high frequency detail from any previously described. These new force components have been found to have significant correlation with other events of the cardiac cycle. The observation that various cardiodynamic aberrations alter these forces in a predictable manner offers the possibility of a more rational interpretation of the ballistocardiogram. The present study was designed to verify the reproducibility of the force pattern in young normal subjects, and to examine the apparent correlation between the ballistic deflections and certain measurable events of the cardiac cycle.

From the Department of Medicine, Medical College of Alabama, Birmingham, Alabama, and the Veterans Administration Hospital, Birmingham, Ala.

Aided by grants from the U. S. Public Health Service, The Life Insurance Medical Research Fund, and the Ingco Foundation.

Drs. Hefner and Jones are Trainees of the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

Methods

The force ballistocardiograms of 20 young normal subjects were recorded from the ultra low frequency system previously described.[6] This ballistocardiograph is based on the principle of the horizontal pendulum and has a gross weight of 12 pounds. The motion of the bed is sensed as acceleration by a modification of the mercury-sulfuric acid capillary accelerometer, as described by Elliott and associates.[7] The upper limit of the calculated linear frequency response of the entire system varies with the square root of the weight of the subject, and ranges from 30 c.p.s. for the lightest subjects to approximately 40 c.p.s for the heaviest.[6] The increased frequency response is in part dependent on the use of a footboard and shoulder straps, to increase the coupling of the body to the bed.

The electrocardiogram, carotid pulse wave, and heart sounds were simultaneously recorded with the ballistocardiogram by a Sanborn Poly-Viso Recorder. The carotid pulse was sensed with an Infraton* arterial pickup, using the Control Model E. The heart sounds were recorded by a Sanborn microphone into a Sanborn D-C amplifier. Frequencies over 60 c.p.s. are attenuated by this heart sound system, but the system is adequate for timing the major components of the heart sounds.

For each subject the intervals between the Q wave of the electrocardiogram and each of the consistent deflections of the ballistocardiogram were measured in 5 cycles, taken with respiration suspended at the end of normal expiration. The intervals between Q and the first major vibration of the first heart sound and the 2 major components of the second sound, the upstroke of the carotid pulse, the anacrotic shoulder of the carotid pulse, and the carotid incisura were similarly measured from the same cycles. To facilitate an understanding of the relationship

* Made by Medical Electronics Development Company, Great Neck, N. Y.

between the carotid pressure pulse and the force ballistocardiogram, the carotid pulse wave was graphically differentiated in a few subjects. The pulse wave itself may be considered as a record of displacement, the first derivative as velocity, and the second derivative as acceleration of pressure change. The anacrotic shoulder of the carotid pulse was taken as the segment of most rapid slope change at the top of the initial upstroke. This was found to correspond to the point of maximal initial deceleration of the second derivation of the carotid pressure pulse.

Results

The ballistocardiograms of normal young subjects are strikingly similar, showing consistent and repetitive wave forms. Figure 1 illustrates a typical complex drawn with all the points labeled. Figure 2 is an illustration of the tracings made on 4 young normal subjects with simultaneous electrocardiogram, heart sound, and carotid pressure pulse.

The terminology used subsequently in the description of the ballistocardiographic pattern is a modification of the conventional system, necessitated by the multiplicity of points that require names for descriptive purposes.*

It is not intended as a proposal for a final nomenclature, but rather is used to illustrate more clearly the concepts as to the genesis of the various deflections. The subscripts R or L are used when the peak force so labeled can be confidently ascribed to a definite event occurring in the right or left side of the circulation. A number of points are not labeled, since evidence as to their origin is not presently available.

The normal ballistocardiogram is characterized by a slow small inconstant footward force (the F-G wave) during early systole, which is interrupted by a headward force terminating at a sharp point (termed H_R) at .085 second ($\pm$.010) after Q. This is followed by a sharp footward deflection which is interrupted by a headward deflection that reaches a peak (termed H_L) at .116 second ($\pm$.013 after Q). This headward force is usually clearly defined, although in some tracings it is indicated only as a slur on the downstroke. From the H_L point, the force vector resumes its footward direction to a nadir (termed I_L) at .142 second ($\pm$.015 second) after Q. Very close to this time in many normal records (36 out of the 100 normal complexes measured), there is a small headward force (I+). The major headward force that follows has 3 distinct components, the peaks of which are labeled J_R, J_L, and J_D. J_R and J_D are variable as to amplitude and timing, depending in J_R on the relationship of the measured complex to the phase of the respiratory cycle. The time of these points from the Q wave are: J_R—.177 second $\pm$.019; J_L—.217 $\pm$.019 second; and J_D—.250 $\pm$.027 second. The J_D point is present in about two-thirds of the complexes from the young normal subjects. Following the last J peak (J_D) there is a relatively slow decay in the headward force. This is followed by the K point, which is .305 $\pm$ .024 second after the Q wave. The K point is variable as to position and time. Following this variable portion of the ballistocardiographic complex there is a sharp headward peak (L_L) occurring .39 $\pm$ .03 second after Q. This is usually succeeded by 2 footward forces separated by a small but sharp headward peak (L_R) occurring .41 + .03 second after Q. Sometimes these 2 footward forces are apparently superimposed. The earliest diastolic force is slow and diphasic, with the first element

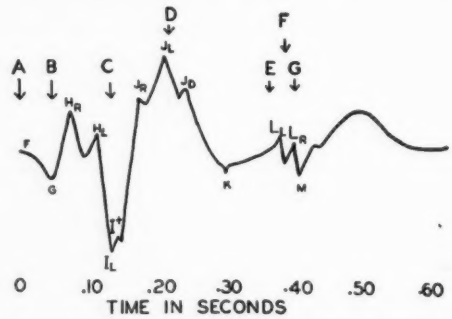


FIG. 1. Diagrammatic illustration of the normal ballistocardiogram with the major deflections labeled. The physiologic events are indicated by numbers, as follows: *A*, onset of Q wave; *B*, time of first major deflection of first heart sound; *C*, time of carotid upstroke; *D*, time of the carotid shoulder; *E*, time of first component of the second heart sound; *F*, onset of second component of the second heart sound; and *G*, carotid incisura.

* We are indebted to Dr. Isaac Starr for helpful criticism relative to the nomenclature of the ballistocardiogram.

headward, while the remainder of the diastolic forces in normal subjects are inconstant and of small amplitude and low frequency. The atrial forces are normally of small magnitude and have not been considered here.

The time relationships of these points in 20 normal subjects are presented in table 1. Five complexes from each subject made during held expiration were measured. The mean, range, and standard deviation for each measured phenomenon are given. In addition, measurements from the onset of the QRS complex to the first major deflection of the first heart sound, the carotid upstroke, the carotid shoulder, the beginning of the second heart sound, and the beginning of the second component of the second heart sound are included. The first major deflection of the first heart sound begins at .056 ± .015 second after Q, and was observed to correlate well with the beginning of the G-H upstroke of the ballistocardiograph. The

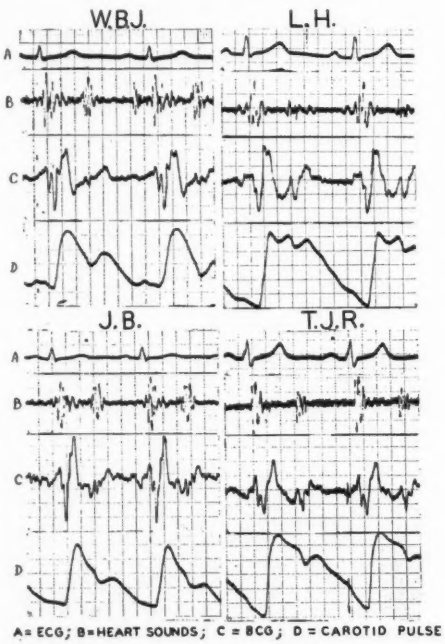


FIG. 2. Representative records taken on 4 young normal subjects. The electrocardiogram, heart sounds, carotid pulse, and ballistocardiogram are shown. Notice the consistent patterns and the sharp points. Paper speed is 50 mm. per second. The heavy time lines are at .10-second intervals.

H_R point was not found to correlate with the other events measured. The H_L point in all cases preceded the carotid upstroke from .01 to .04 second (mean .017 ± .007 second). The I_L point (.142 ± .015 second after Q) was found to correlate with the initial positive acceleration peak of the carotid pressure rise in a few subjects from whom these data were obtained by graphic differentiation of the carotid pressure pulse (figure 3). Furthermore, previous work from this laboratory has already established the time of this acceleration peak obtained from carotid pressure pulses in 10 normal subjects as occurring at .14 second after the Q.[8]

Figure 3 shows a comparison of the ballistocardiograph, the carotid pulse, and the graph-

TABLE 1.—*Ballistocardiographic Times and Correlation with Other Events*

	Mean ± S.D.	Range	No. of Observations
Q-S_1	.055± .015	.03– .09	100
Q-H_R	.085± .010	.06– .10	100
Q-H_L	.116± .013	.08– .14	99
Q-CU	.134± .014	.11– .16	100
Q-I_L	.142± .013	.12– .17	100
Q-I_+	.142± .015	.11– .17	36
Q-J_R	.177± .019	.14– .22	95
Q-J_L	.217± .019	.18– .26	100
Q-CS	.221± .022	.18– .28	95
Q-J_D	.250± .027	.21– .32	58
Q-K	.305± .024	.26– .37	86
Q-L_L	.39 ± .03	.33– .46	100
Q-L_R	.41 ± .03	.35– .48	76
Q-Cin	.41 ± .03	.34– .48	99
Q-S_{2a}	.37 ± .03	.31–.44	100
Q-S_{2b}	.40 ± .03	.35– .46	74
H_L-CU	.017± .007	.10– .04	99
J_L-CS	.003± .009	−.03–+.03	95

Data were obtained from measurements of 100 complexes from 20 subjects. The mean, standard deviation, and range for each series of measurements are given. The right hand column gives the number of the individual waves present in the total 100 complexes. The points measured are from the onset of the QRS complex (Q) to the first major deflection of the first heart sound (S_1); to the initial upstroke of the carotid pulse wave (CU); to the shoulder of the carotid pulse wave (CS); to the carotid incisura (Cin), and the first and second components of the second heart sound (S_{2a} and S_{2b}). Also, measurements are made from Q to the ballistocardiographic points, as indicated.

ically determined second derivative (or acceleration tracing) of the carotid pulse. The variable I_+ point, when present, occurs at a time closely related to the onset of the carotid upstroke. The J_R peak was found to vary with respiration in magnitude and, to some extent, in time. It does not correlate with events in the carotid pulse. The J_L peak, on the other hand, was found to be almost synchronous with the anacrotic shoulder of the carotid pulse (carotid shoulder). The carotid shoulder was taken as the point of maximal deceleration of the carotid pulse pressure rise, and could be selected with fair accuracy from simple inspection of the carotid pulse curve. Figure 3 clarifies the relationship of the carotid shoulder and the point of maximal deceleration of the carotid pulse. A temporal relationship between the shoulder of the carotid pulse and one of the high frequency J peaks has been noted by Rappaport.[9] Similarly, the J_D point may be related to slope changes of the carotid pulse in late systole. This slope change is visible in figure 8. The subscript D indicates the delayed J wave. The K point has not been shown to be related to the physiologic events as measured. The 2 L peaks, L_L and L_R, have a close relationship to the first and second components of the second heart sound. L_L occurs during the rapid downstroke of the carotid incisura, at the time of the first component, and L_R occurs slightly later with the second component of the second sound.

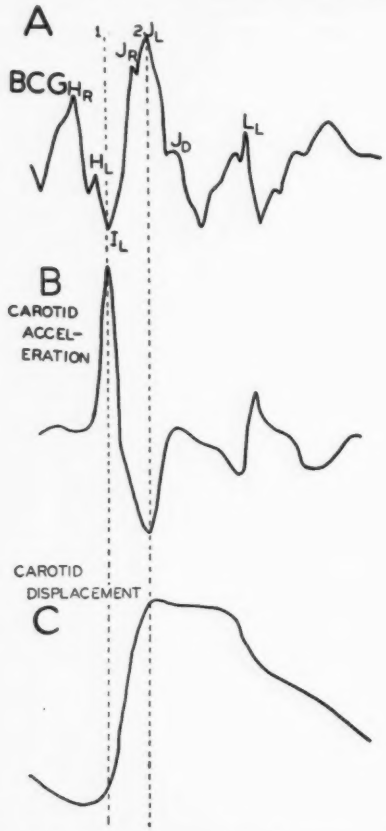


FIG. 3. A diagram of a carotid pulse compared with the graphically determined second derivative of the carotid pulse and the ballistocardiogram. Notice that the point of maximal acceleration of the carotid pulse (as determined by its second derivative or acceleration curve) corresponds in time to the I_L point of the ballistocardiogram. Also, the point of maximal deceleration of the carotid pulse corresponds to the J_L point of the ballistocardiogram. Connecting lines (labeled 1 and 2) on the above graph illustrate this relationship. Notice that the segment of most rapid slope change on the carotid pulse curve corresponds to the point of maximal deceleration on the second derivative curve.

A striking correlation was found between the times of H_R and H_L and the reported times of right and left ventricular ejection, respectively. In 10 subjects studied by cardiac catheterization, Braunwald, Fishman, and Cournand[10] found the interval between the onset of the Q wave of the electrocardiogram and right ventricular ejection to be .080 ± .0079 second. This is to be compared to a Q to H_R time of .085 ± .010 second in the present study. Braunwald's value for Q to left ventricular ejection time is .115 ± .0117 second in 12 subjects, as compared to a Q to H_L time of .116 ± .013 second found in the present study.

PHYSICAL CONSIDERATIONS

Acceleration tracings from an ultra low frequency ballistocardiographic system are representations of cardiovascular force, unless there is distortion imposed by the internal body network as mentioned by von Wittern.[1] Such distortion does not appear to alter the time relationship of the transmission of force, since the ballistocardiographic waves correlate in time with physiologic events in an entirely reasonable manner, as the present study demon-

strates. Since the acceleration ballistocardiograph from an ultra low frequency system represents cardiovascular force, one must interpret such tracings according to the physical laws concerning force. Newton's second law of motion relates force, mass, and acceleration according to the equation: force equals the product of mass times acceleration. Newton's third law of motion states that for every force there is a simultaneous equal and opposite force. In the case of a low frequency ballistocardiograph in the head-foot axis, the subject is essentially isolated from the environment so far as head-foot forces are concerned. It is, therefore, necessary that for every headward force registered in the ballistocardiograph, a net footward force of equal magnitude exists within the body, and conversely, every footward force in the ballistocardiograph represents a net headward force within the body. Briefly then, one must search for the *opposite* forces within the cardiovascular system to elucidate each ballistocardiographic deflection. In considering the genesis of a headward wave, then, the only reasonable thesis must predicate a net footward force (or mass acceleration) in the cardiovascular system. This implies nothing about the actual direction of motion of the cardiovascular mass, since the deceleration of a headward motion represents the same kind of force as the acceleration of a footward motion.

Application of Physiologic and Physical Considerations

Pre-ejection Systole (Onset of QRS to Left Ventricular Ejection). In normal subjects there is sometimes a small footward force, having its onset prior to the first heart sound. In normal subjects this wave (the F-G wave) is not often visible, and was, therefore, not measured. This wave, however, has been observed to be exaggerated in certain abnormal states, notably those with enlargement of the right ventricle, such as mitral stenosis and cor pulmonale (fig. 4). A similar early presystolic force has been described by others, using high frequency technics.[11, 12] It has been observed to be present with atrial fibrillation, showing its independence from atrial systole.

Following the F-G wave, there is a headward deflection or force having its onset at approximately .05 second after Q. The time of onset correlates with the first major vibration of the first heart sound, and this upstroke (the G-H wave) has been observed to be exaggerated in patients with mitral stenosis, and other conditions causing pulmonary hypertension (fig. 4).

It is postulated that the initial event at the onset of right ventricular contraction is an acceleration of an impulse or "bolus" of blood toward the base of the heart.* This headward acceleration of blood would result in a footward force on the body (the F-G downstroke). The subsequent deceleration (footward acceleration) resulting from the impact of this "bolus" against the closed A-V and semilunar valves would result in a headward acceleration of the body. When the impact force on the pulmonic valve has become sufficiently great to open the valve, there is a sharp headward acceleration of the now unimpeded pulse wave as it flows into the pulmonary artery. This is reflected by a footward acceleration of the body in reaction, causing the downstroke following the H_R point. Meanwhile, an analogous headward force has begun on the left side of the heart because of impact on the aortic valve, and terminates when the aortic valve opens, normally somewhat later than the opening of the pulmonic valve. This impact produces a visible headward deflection in the force ballistocardiogram terminating at the H_L point. The pulse wave then is accelerated headward in the aorta, producing a footward reaction on the body, the H_L-I_L downstroke.

Ejection Systole. The H_L point occurs at the time of left ventricular ejection, as measured by Braunwald[10] and as may be predicted from the time of the upstroke in the carotid pulse. The subsequent footward force on the body would be the anticipated reaction to the headward acceleration of blood in the aorta. The ejection from both ventricles contributes to this force, since the ejection from the right ventricle is still present. The correlation of the

* This peristaltic-like activity of the myocardium was first described by Harvey, and is visible in high speed cinemographs of the heart,[13, 14] though this kind of heart motion in the intact dog has been challenged by Anzola.[15]

I_L point in time with the point of maximal initial acceleration of the carotid pulse has been of great interest. The similarity of the force ballistocardiogram and the inverted second derivative of the carotid pressure pulse, as regards both relative amplitude and time, is strikingly demonstrated by figure 3.

Directly recorded second derivatives of the carotid pulse have been obtained from this laboratory, and demonstrate the similarity.[8] The implications of this similarity are discussed below. The fact that the I_L point of the ballistocardiogram coincides so closely with the point of maximal initial acceleration of the carotid pressure pulse constitutes evidence that the I_L point is related to the point of maximal acceleration of left ventricular ejection. The H_L-I_L downstroke, then, may prove to be a most important representation of the accelerator function of the left ventricle, since, as is shown below, the later waves may be more influenced by extracardiac factors.

The I_+ wave, although measurable in only one third of the normal complexes, has repeatedly been found to be exaggerated in various abnormal states (fig. 5). Its relationship to the carotid upstroke has suggested the possibility that it is related to the initial propagation of the pulse wave into the arch of the aorta.

To facilitate description, the J_L point is discussed before J_R. The J_L point is clearly related to the shoulder of the carotid pulse. Not only is the temporal correlation excellent in our normal subjects, but also in all of the abnormalities thus far studied. The carotid shoulder, as is shown in figure 3, is the point of maximal negative acceleration or deceleration of the carotid pulse. Its magnitude and duration are affected by alterations in aortic elasticity as well as by the acceleration of ejection.[16] The force of deceleration is increased, and comes earlier in instances of increased aortic rigidity. This is reflected by a steep slope of the carotid pulse with the carotid shoulder occurring earlier in the cardiac cycle than is normally the case. Figure 6 illustrates the observed type of ballistocardiographic alteration in such an instance. The carotid upstroke is steep, with an early shoulder correlating precisely with an early J peak in the ballistocardiogram. It should be noted that J_L, the peak corresponding to the carotid shoulder, is now the earliest of the prominent J points. The desirability of physio-

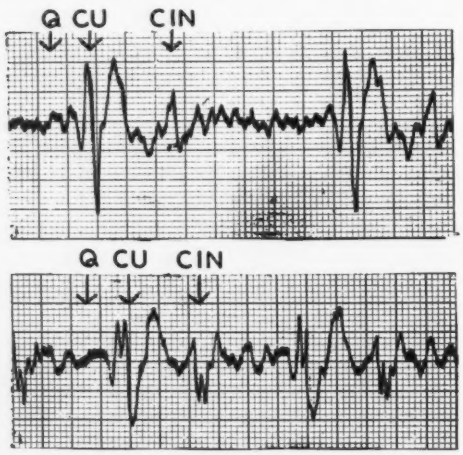


FIG. 4. The top tracing was taken on a patient with mitral stenosis. The bottom one was taken on a patient with pulmonary hypertension. Both patients were thought to have right ventricular hypertrophy, clinically. The times of the Q onset, the carotid upstroke, and the carotid incisura are indicated. Note the prominence of the F-G and G-H segments. The first major negative deflection after Q is the F-G segment. Paper speed is 50 mm. per second.

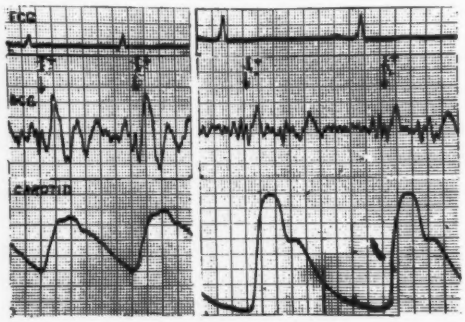


FIG. 5. These 2 ballistocardiographic tracings illustrate the prominence of the I_+ point seen occasionally in records from patients with heart disease. The first tracing is from a patient with an old myocardial infarction; the second is from a patient with myocarditis, cause unknown. Notice in the second record that the Q to H_R, Q to H_L, and Q to carotid upstroke times are all delayed in comparison to normal subjects. Paper speed is 50 mm. per second.

logic, rather than sequential identification of the various deflections is strikingly apparent in such records.

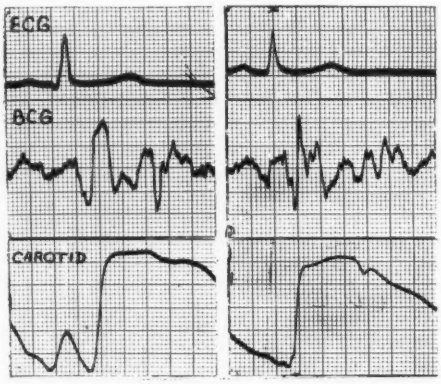


FIG. 6. The left figure is from a normal subject with a slow heart rate and a Q to carotid upstroke time of .16 second. Notice that the J_L point and the carotid shoulder coincide in time. The second tracing was taken from a patient with hypertension. Here, the Q to carotid upstroke time is unusually short (.10 second). However, the J_L point still coincides with the carotid shoulder as it did in the previous instance. Paper speed is 50 mm. per second.

The relationship of the carotid pulse as an index of mass acceleration in the central arterial system and the systolic waves of the force ballistocardiogram demonstrates the importance of the arterial pressure pulse as a factor in the genesis of the ballistocardiogram. This relationship is as anticipated. The carotid pulse may be regarded as reflecting changes in mass displacement due to the surge of blood in the arterial system, so that the headward surge of ejection produces an upstroke, and the predominantly footward surge of run-off produces a downstroke. The second derivative of the carotid pulse, then, represents the accelerations of this pulse wave motion. The reaction on the body, according to Newton's third law of motion, requires that the curve be inverted to correspond to the ballistocardiographic deflections. One would expect the second derivative of the carotid pulse to correlate with the ballistocardiogram only to the extent that the carotid pulse represents a summation of the movements of blood in the arterial system. Local turbulence in the carotid artery would obscure the close relationship between the in-

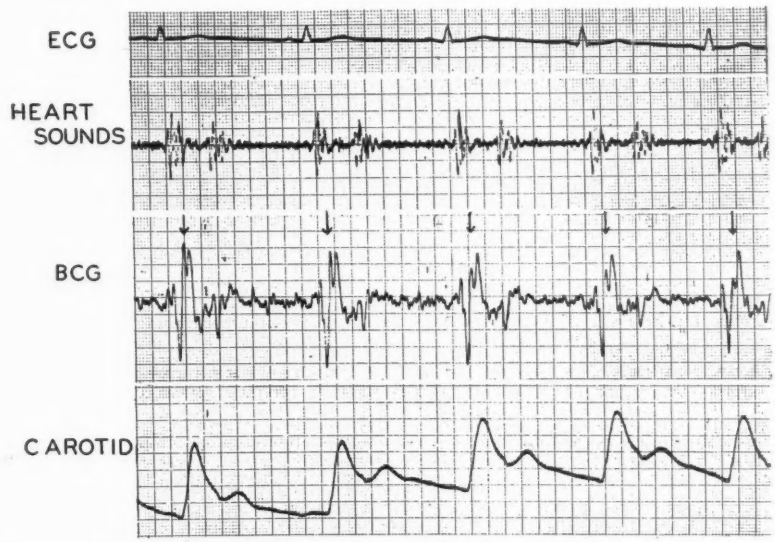


FIG. 7. This tracing was taken on a normal subject during held inspiration. Recording was begun as soon as the patient had inspired. Notice that the J_R point (*arrow*) is initially the major J point, and that it gets progressively smaller as the breath is held. It is also of interest that the footward segment following H_R varies in the same manner. Paper speed is 50 mm. per second.

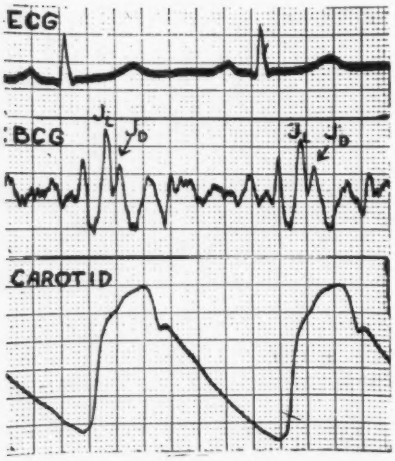


FIG. 8. This tracing was taken on a 60-year-old man without clinical evidence of heart disease. Notice the prominence of the J_D point. Similar patterns have been seen in older aged, normal subjects and in subjects with atherosclerosis. The striking relationship of J_L to the anacrotic shoulder of the carotid pulse is clearly evident.

verted second derivative of the carotid pressure pulse and the left ventricular waves of the ballistocardiogram.*

The above considerations make it apparent that the amplitude and contour of the J wave may be changed by noncardiac factors, since the contour of the arterial pressure pulse is profoundly affected by such factors as elasticity of the vessel walls and viscosity of blood.

The J_R point, which normally precedes the J_L point described above, has no apparent relationship to the carotid pulse. It has been observed to vary markedly with respiration, increasing in amplitude with inspiration and decreasing with expiration. Also, on held deep inspiration this point may be initially the major J wave, becoming progressively smaller as inspiration is held. This corresponds to the increase in right ventricular output which is presumed to be present initially during inspiration (fig. 7). Because of these findings, the J_R point is thought to be due to the maximal impact of blood from the right ventricle on the pulmonary artery bifurcation. This is analogous to the J_L point, thought to represent the maximal impact of ejection from the left ventricle on the arch of the aorta. (The term "impact" as used in the above statements, is synonymous with a rapid deceleration of blood, the term used in the discussion of the J_L wave.)

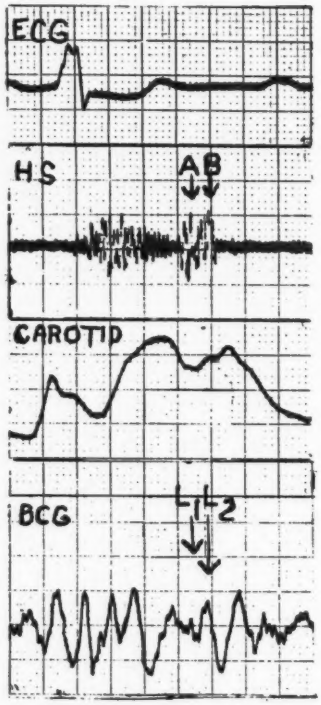


FIG. 9. This record was obtained from a patient with an atrial septal defect. Notice the complex early systolic pattern and the wide splitting of the L points. The major L point is the second one corresponding in time to the second component of the second heart sound, and coming after the carotid incisura. Paper speed is 50 mm. per second.

The J_D point is an inconstant peak seen in about half of the young normal subjects (58 out of 100 complexes). It has been observed to be much more prominent in older normal subjects, and particularly in subjects with arteriosclerotic heart disease (fig. 8). The mechanism of this deflection is not well understood, but because of its prominence in older subjects,

* Nyboer, Watson, and Hanover[17] have demonstrated a striking relationship between the mass displacement ballistocardiograph (second integral of force) and the body plethysmograph. The present study, relating this force ballistocardiograph to the acceleration of the carotid pressure pulse, supports this concept.

and its correlation with slope changes in the carotid pressure pulse, it is thought to be related to physical factors of the arterial system, and to the relative magnitude of late systolic ejection.

The J-K downstroke is probably related to at least 2 factors: to the termination of headward force after J_D, and to the impact of the pulse wave on the peripheral arteries.

Diastolic Period (Beginning with the Onset of the Second Heart Sound). The L peaks are closely related to the second heart sounds. The headward forces, reaching their maximum at the L peaks, are postulated to be due to the brief reversal of flow above the semilunar valves on reversal of the pressure gradient at the end of systole. The L-M downstrokes are thought to be due to the impact of blood on the semilunar valves as they close. Figure 9 shows a tracing taken from a patient with an interatrial septal defect. Notice that the second sound is widely split. Synchronous with the second component of the second heart sound, and following the carotid incisura, there is a large footward deflection. Because of this time relationship and the exaggeration of the second component, the first segment is thought to be due to aortic valve closure, and the second to pulmonic valve closure. This wide splitting of the L points has been observed in subjects with widely split second sounds. In subjects without splitting of the second sound, on the other hand, the L-M waves are very close together, or even superimposed.

Discussion

The points on the force ballistocardiogram described above are those that are consistently seen in records taken on young normal subjects. However, in individual complexes, there are at times minor deflections that are without obvious correlation with the events of the cardiac cycle. Also, in tracings from patients with altered cardiovascular dynamics, the normally present deflections may be diminished, increased, or shifted in time. In such cases, it is necessary to relate the deflections of the ballistocardiogram with other events, such as the heart sounds, the electrocardiogram, and the carotid pulse, in order to identify the deflection. In some patients with heart disease, there are ballistocardiographic forces that are not readily identified by the above technics. These may be due to abnormal movements of the heart itself, or to a grossly distorted sequence of contraction.

The mechanisms postulated for the genesis of the ballistocardiographic waves are undoubtedly an oversimplification. The primary mechanisms considered are those due to forces caused by acceleration and deceleration of blood. Since any mass acceleration within the body contributes to the total registered force, acceleration of the myocardium itself must make some contribution to the genesis of the force ballistocardiogram. The fact that a force ballistocardiographic complex is obtained with the blood inflow clamped off has been previously reported from this laboratory, and demonstrates that under some circumstances acceleration of the myocardium may play an appreciable role in the ballistocardiographic genesis.[18] In addition, since the head-foot ballistocardiogram records only the head-foot force vector and may be a measurement of the summation of multiple simultaneous forces, some cancellation of forces and some summation of forces may be expected. These factors would, of course, make it difficult to attribute a particular wave as being entirely due to a specific force. However, because of the consistency of the normal ballistocardiographic pattern and the easily recognized, even anticipated changes seen in the records obtained from many abnormal subjects, it is considered that an analysis of the wide frequency range force ballistocardiogram will give considerable information about the timing and relative magnitude of cardiovascular events.

Summary

The force ballistocardiograms of 20 normal subjects, as recorded from an ultra low frequency system having an extended frequency range, are described. These tracings were found to have high frequency components not previously described. The ballistocardiographic forces are considered in terms of other physiologic events. Distinct footward forces are found at the time of right and left ventricular ejec-

tions. The IJK segment can consistently be separated into 3 and sometimes 4 components. One of these is related to the anacrotic shoulder (the acceleration transient) of the carotid pulse and is considered to be due to deceleration of the initial ejection in the aortic system. Another J component can be related similarly to the pulmonary circulation. Major footward forces correlate in time to the asynchronous closure of the aortic and pulmonic valves.

The mechanism of the production of such forces is considered in terms of physical laws of force as related to accelerations and decelerations of the cardiovascular system.

Ballistocardiograms from patients with various cardiovascular phenomena are presented in terms of the known alterations of cardiovascular physiology. It is found that the ballistocardiographic changes present in these instances are consistent with the hypothesis offered of the genesis of the ballistocardiographic deflections.

Summario in Interlingua

Es describite le ballistocardiogramma de fortia registrate ab 20 subjectos normal per medio de un systema a frequentia ultrabasse con extension del gamma de frequentias. In iste registrationes, componentes de alte frequentia esseva trovate que non es describite in ulle previe publication. Le fortias ballistocardiographic es considerate in relation a altere evenimentos physiologic. Distincte fortias pedorse es trovate al tempore del ejectiones dextero- e sinistro-ventricular. Le segmento IJK pote regularmente esser separate in 3 e a vices in 4 componentes. Un de iste componentes es relationate al nivello anacrotic (le transiente de acceleration) del pulso carotic e pote esser interpretate como effecto del deceleration del ejection initial a in le systema aortic. Un altere componente J pote esser relationate similemente al circulation pulmonic. Major fortias de direction pedorse es temporalmente correlationate al clauditura asynchrone del valvulas aortic e pulmonic.

Le mechanismo del production de tal fortias es considerate super le base del leges physic de fortia, applicate al accelerationes e decelerationes del systema cardiovascular.

Es presentate balistocardiogrammas ab patientes con varie conditiones cardiovascular, con attention prestate al alterationes cognoscite del physiologia cardiovascular. Es constatate que le alterationes ballistocardiographic que occurre in iste casos es de accordo con le hypothese hic formulate in re le genese del deflexiones ballistocardiographic.

REFERENCES

[1] von Wittern, W. W.: Ballistocardiography with elimination of the influence of the vibration properties of the body. Am. Heart J. **46:** 705, 1953.

[2] Talbot, S. A., and Harrison, W. K.: Dynamic comparison of current ballistocardiographic methods. I. Artifacts in the dynamically simple ballistocardiographic methods. Circulation **12:** 577, 1955. II. Effect of a platform in ballistocardiographic dynamics. Ibid., p. 485; III. Derivation of cardiovascular force from body motions. Ibid., p. 1022.

[3] Honig, C. K., and Tenney, S. M.: The relationship between the ballistocardiogram, cardiac movement, and blood flow. Am. Heart. J. **52:** 167, 1956.

[4] Tucker, W. T., and Ostrom, E. J.: The effects of progressive damping and other technical procedures on the direct displacement ballistocardiogram. Am. Heart. J. **49:** 21, 1955.

[5] Hoffman, I., Kissin, M, and Schwarzchild, M. M.: Oscillation-free ballistocardiography, a simple technic and a demonstration of its validity. Circulation **13:** 905, 1956.

[6] Reeves, T. J., Jones, W. B., and Hefner, L. L.: Design of an ultra low frequency force ballistocardiograph on the principle of the horizontal pendulum. Circulation **16:** 36, 1957.

[7] Elliott, R. V., Packard, R. G., and Kyrazis, D. T.: Acceleration ballistocardiography; design, construction and application of a new instrument. Circulation **9:** 281, 1954.

[8] Neal, J. J., and Reeves, T. J.: The direct recording of the first and second derivatives of the arterial pulse in man. In preparation.

[9] Rappaport, M. B.: Considerations in ballistocardiography. Mod. Concepts Cardiovas. Dis. **24:** 6, 1955.

[10] Braunwald, E., Fishman, A. P., and Cournand, A.: Time relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man. Circulation Research **4:** 100, 1956.

[11] Davis, F. W. Jr., Scarborough, W. R., Mason, R. E., Singewald, M. L., and Baker, B. M.: The ballistocardiogram in mitral stenosis. Circulation **7:** 503, 1953.

[12] Tucker, W. T., Knowles, J. L., and Eddleman,

E. E., JR.: Mitral insufficiency: Cardiac mechanics as studied with the kinetocardiogram and ballistocardiogram. Circulation **12:** 278, 1955.

[13] HARVEY, W.: Exercitatis Anatomica de Motu Cordis et Sanguinis in Animalibus. London, 1628.

[14] SMITH, L. A., FIELDS, J., KENNAMER, R., AND PRINZMETAL, M.: Studies on the mechanism of ventricular activity. III. Contraction of the vestricles in experimental bundle branch block. Am. Heart J. **44:** 231, 1952.

[15] ANZOLA, J.: Right ventricular contraction. Am. J. Physiol. **184:** 567, 1956.

[16] PETERSON, L. H.: The dynamics of pulsatile blood flow. Circulation Research **2:** 127, 1954.

[17] NYBOER, J., WATSON, T. R., AND HANOVER, N. H.: Constant mass displacement ballistocardiography and electrical impedance plethysmography. J. Lab. & Clin. Med. **46:** 270, 1955.

[18] THOMAS, H. D., FREDERICK, W. H., KNOWLES, J. L., REEVES, T. J., PAPPAS, R., AND EDDLEMAN, E. E. JR.: Effects of occlusion of the venae cavae, aorta, and pulmonary artery on the dog ballistocardiograph. Am. Heart. J. **50:** 424, 1955.

Orgain, E. S.: Pheochromocytoma: The Value of Certain Tests Used Routinely in Diagnosis. Ann. Int. Med. **43:** 1178 (Dec.), 1955.

Pheochromocytoma is a relatively uncommon but surgically curable condition. It is a chromaffin type of tumor that masks itself under various forms, notably hypertensive vascular disease. Several clinical features can suggest its presence including fever, tachycardia, respiratory disturbances, glycosuria, and hypermetabolism. The practical value of various pharmacologic tests in regard to their diagnostic usefulness have been analyzed in connection with this particular entity. This report is based not so much on the medical literature as on our own experience. The author especially recommends the use of provocative tests employing histamine, tetraethylammonium or methacholine for patients who exhibit paroxysmal hypertension and adrenergic blocking agents such as phentolamine or piperoxan for the routine screening of the patients who have a persistent elevation of the blood pressure. The factors responsible for false positive or false negative tests that have been encountered in examining such cases, have been discussed. There is presented a description of the technic of the tests, of the selection of patients, and of the criteria for a positive test. Certain conclusions seem to be justified: (1) no single pharmacologic test is considered confirmatory in the diagnosis of the condition, (2) the tests are to be performed only after intelligent selection of patients is made, (3) the nature of the results, whether positive or negative, indicates the necessity for additional tests by additional drugs to confirm or exclude the diagnosis, (4) all patients below the age of 60, in whom there is continuous elevation of the blood pressure, deserve the routine use of such screening tests to exclude pheochromocytoma.

WENDKOS

Anomalous Connection of Right Pulmonary Veins to Superior Vena Cava with Interatrial Communications

Hemodynamic Data in Eight Cases

By H. J. C. Swan, John W. Kirklin, Luis M. Becu, and Earl H. Wood

Anomalous connection of the right pulmonary veins to the superior vena cava associated with an interatrial communication in an unusually cephalad location has been diagnosed at cardiac catheterization in 8 patients. These patients had the clinical features seen in patients who have atrial septal defects in the region of the fossa ovalis. Differentiation was accomplished by (1) the roentgenographic position of the catheter in the right superior pulmonary vein, (2) demonstration of an abnormally high oxygen saturation of the blood in the superior vena cava, (3) the presence of a small right-to-left shunt from the superior vena cava and the absence of such a shunt from the inferior vena cava, and (4) demonstration of similar drainage of blood from the right superior pulmonary vein and superior vena cava. The syndrome is considered to be an anomaly of pulmonary venous development while the atrial septum forms normally.

RECENT advances in surgical technics have made possible the closure of communications between the right and the left atria. Study and treatment of patients with such cardiac anomalies have shown that many varieties of interatrial communication may exist. Since the technic of closure may differ considerably according to the type of communication present, the identification of these varieties is of both practical and academic interest.

A variant of interatrial communication considered to be rare by anatomists and pathologists is the association of an anomalous connection of some or all of the veins of the right lung with the superior vena cava, or with the caudal portion of this vessel and the cephalad portion of the right atrium, and an interatrial communication located cephalad to the fossa ovalis near the site of the anomalous connection. The fossa ovalis is usually intact, but an atrial septal defect in this region may coexist. With the relatively large number of cases now reported, it is clear that this anomaly is unusual but not rare. In a series of 35 patients with interatrial communications treated surgically, Lewis and associates[1] clearly recognized and described this anomaly in 3 patients and reasoned that it was present in 2 others.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Three anatomic features characterize the anomaly: (1) the defect is above the fossa ovalis and separate from it; (2) no margin of tissue is present superiorly between the defect and the superior vena cava and an incomplete one is seen posteriorly; and (3) there is an associated anomalous connection of the right superior and, at times, the inferior pulmonary veins. We found no information of hemodynamic significance on this condition in the literature.

The hemodynamic state existing in such patients may be clarified by use of the term "connection" to define an anatomic relationship and of the term "drainage" to indicate a functional or physiologic connotation.[2, 3] Anomalies with normal drainage of blood from the pulmonary vein to the left ventricle by anomalous pathways have been described.[4] In contrast, the functional anomaly usually present in patients with large interatrial defects in the region of the fossa ovalis in whom the right pulmonary veins are normally connected to the left atrium is similar to that in patients who have interatrial communications and anomalously connected pulmonary veins. Use of "connection" and "drainage" facilitates the description of the complex functional derangements associated with many of the varieties of interatrial communication, which are not determined on the basis of anatomic malformation alone.

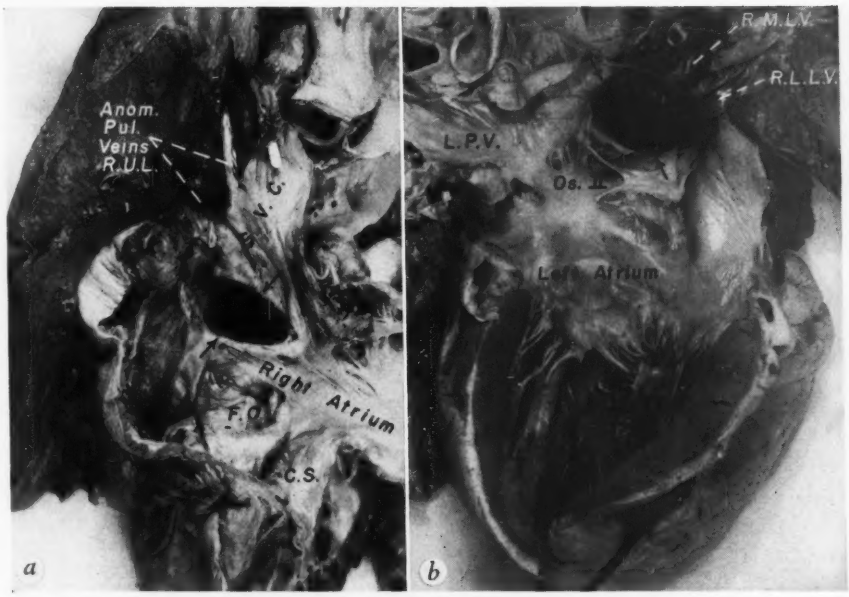


FIG. 1. Anatomic features of heart with high atrial septal defect and anomalous connection of right upper lobe pulmonary veins to superior vena cava (specimen provided by courtesy of Dr. J. E. Edwards). *a*. View from right atrium. Note particularly location of the large interatrial communication (between arrows) above the fossa ovalis (*F.O.*) and straddled by the superior vena cava (*S.V.C.*), into which 2 veins from the upper lobe of the right lung (*R.U.L.*) connect. The left atrial orifice of the pulmonary vein from the middle lobe can be seen at the left upper margin of the defect. Probe is in azygos vein. *C.S.* = coronary sinus. *b*. View of same heart from left side. Note large interatrial communication and left pulmonary vein (*L.P.V.*). The veins from the middle and lower lobes (*R.M.L.V.* and *R.L.L.V.*) of right lung drain into the left atrium at the interatrial defect.

This paper is concerned with hemodynamic data and their interpretation in 8 patients studied at the Mayo Clinic and considered to have anomalous connections of some or all of the right pulmonary veins to the caudal portion of the superior vena cava, with an associated "high" interatrial communication. The diagnosis in each patient was made at cardiac catheterization. Cardiotomy was carried out in 6 of these patients and the diagnosis was confirmed.

Correction of the anomalies was successfully accomplished with survival in 5 of the 6 patients just mentioned. In the sixth patient (case 6), who had severe pulmonary hypertension, the defect was not repaired because temporary occlusion of the interatrial communication at the time of operation resulted in an increase in pulmonary arterial pressure and a decrease in radial arterial pressure. This patient subsequently died but necropsy was not done. Hence, postmortem studies are not available for any of these patients. A specimen provided by one of our colleagues, Dr. J. E. Edwards, exemplifies the common variant of this anomaly (fig. 1). Hemodynamic studies were not done on this patient. The anatomic findings at the time of thoracotomy in the 6 surgical patients are summarized in table 1 according to the site of connection of the veins from the right lung, the size and location of the principal interatrial communication, and the condition of the fossa ovalis.

In the remaining 2 of the total series of 8 patients, the presence of pulmonary hypertension associated with a great increase in pulmonary vascular resistance and predominant right-to-left shunts was judged to contraindicate surgical repair.

In 4 of the 6 surgical patients (cases 2, 4, 5, and 6), the anomaly was essentially similar to that described by Lewis and associates.[1] In

TABLE 1.—*Anatomic Characteristics of Interatrial Communication and Anomalous Connection of Right Pulmonary Veins*

Case	Location of cardiac connections of right pulmonary veins*		High interatrial communication, location and size (cm.)	Fossa ovalis
	Superior	Inferior		
1	SVC-RA	RA	Posterosuperior aspect of atrium; 3 x 1 (slit)	"Tiny hole"
2	SVC-RA	LA	Superior aspect of atrium; 2.5 x 2	Intact
3	Small diverticulum of left atrium		SVC straddled both atria and diverticulum; 2.5 (circle)	Intact
4	SVC-RA	LA	SVC straddled right and left atria; 2.2 x 1.5	Intact
5	SVC-RA	LA	From SVC caudally to the level of inferior vein connection; 4 x 3	Patent foramen ovale
6	SVC-RA	LA	Superior aspect of atrium; 1 x 0.5	Small defect

* SVC-RA = junction of superior vena cava and right atrium; RA = right atrium; LA = left atrium.

case 1, the superior and inferior pulmonary veins joined to enter the heart through a common orifice at the junction of the superior vena cava with the right atrium. In case 3, a true anomalous connection did not exist; instead, the pulmonary veins all drained to a diverticulum located behind (dorsal to) the junction of the superior vena cava and right atrium. The anterior (ventral) wall of this diverticulum was absent, so that the superior vena cava appeared to straddle both right and left atria and was in free communication with each. Therefore, the only communication between the atria in this patient was by way of the lower part of the superior vena cava above the superior margin of the atrial septum. In case 5, the right superior pulmonary vein connected to the superior vena cava at a point 2 cm. cephalad to the right atrium, while the right inferior pulmonary vein connected to the left atrium. The defect in this patient was larger than in the others, and a separate communication in the fossa ovalis was also present. The principal defect involved the posterior and superior (dorsocephalad) aspect of the interatrial septum, extending 2.5 to 3 cm. caudally from the region of the superior vena cava to the level of the left atrial orifice of the inferior pulmonary vein.

Each patient was sent to the laboratory with the tentative diagnosis of an atrial septal defect. No clinical feature has been recognized that might serve to differentiate this condition from an atrial septal defect of the usual type. Clinical evidence of pulmonary hypertension was present in 3 patients.

METHODS

Cardiac catheterization was carried out in the manner already described from this laboratory.[5, 6] Intracardiac and intravascular pressures were measured by means of strain-gage manometer-catheter systems with adequate frequency and damping characteristics.[7, 8] The oxygen saturation of samples of blood drawn from the chambers of the heart and from the great vessels was determined by means of a cuvette oximeter. Analysis of blood from the heart and from the radial artery as to oxygen content and oxygen capacity was carried out by the method of Van Slyke and Neill.[9] The pulmonary (Q_p) and systemic (Q_s) blood flows (in liters per minute) were determined from the relations:

$$Q_p = \frac{V_{O_2}}{C_{pv} - C_{pa}} \quad \text{and} \quad Q_s = \frac{V_{O_2}}{C_{sa} - C_{mvb}}$$

where V_{O_2} is the oxygen consumption in milliliters per minute, and C_{pv}, C_{pa}, C_{sa} and C_{mvb} represent the oxygen content of pulmonary vein, pulmonary artery, systemic artery, and mixed venous blood, respectively, in milliliters per liter. C_{mvb} was taken as the average oxygen content of superior and inferior caval blood.

The fraction of pulmonary arterial flow representing recirculated blood (S_{1-r}) is given by the relation:

$$S_{1-r} = \frac{C_{pa} - C_{mvb}}{C_{pv} - C_{mvb}}$$

The fraction of systemic artery flow representing mixed venous blood (S_{r-1}) is given by:

$$S_{r-1} = \frac{C_{pv} - C_{sa}}{C_{pv} - C_{mvb}}.$$

Dye-dilution curves were recorded by ear and cuvette oximeters[10] after injection of Evans blue (T-1824) or methylene blue at different locations in the heart and great vessels and are considered in detail in the following section.

TABLE 2.—*Data on Intracardiac Shunts in Anomalous Connection of Right Superior Pulmonary Vein*

Case	Intravascular pressures, mm. Hg*								Blood flow (L./min./M².)		Intracardiac shunt, per cent†	
	LV	Systemic	PA	PV wedge	PV	PA wedge	RV	RA	Pulmonary	Systemic	L-R	R-L
1	‡	105/70	28/16	28/18	13/7	14/10	28/5	5/3	8.4	2.8	67	0
2	117/11	130/75	35/13	12/5	8/2	‡	34/8	7/1	10.6	3.7	66	0
3	107/6	125/70	33/18	25/16	10/6	12/8	28/2	11/8	10.1	5.6	43	0
4	124/11	102/59§	27/13	‡	‡	17/10	58/10	10/0	7.3	3.1	57	0
5	91/0	106/51	86/32	‡	8/0	7/3	81/−2	8/1	4.8	3.5	26	18
6	109/11	113/67	116/43	‡	10/4	11/9	113/6	9/4	2.4	2.5	26	31
7	‡	122/68	113/52	‡	9/4	5/0	113/2	6/2	2.6	2.9	24	30
8	‡	145/84	‡	23/14	8/3	‡	95/8	10/3	‡	‡	0	20

* LV = left ventricle; PA = pulmonary artery; PV = pulmonary vein; RV = right ventricle; RA = right atrium.

† L-R = left-to-right shunt as per cent of pulmonary flow; R-L = right-to-left shunt as per cent of systemic flow.

‡ Not obtained.

§ Systemic arterial pressure recorded 1 hour after left ventricular pressure.

RESULTS

The basic hemodynamic state in these patients is similar to that found in patients who have atrial septal defects. In this small group are examples of large pulmonary blood flow, without pulmonary hypertension, and of severe pulmonary hypertension with bidirectional shunting. It is only in particular hemodynamic details that these patients differ from those who have atrial septal defects of the usual type.

Values of pulmonary flow varied from 10.6 to 2.4 L./min./M.² of body surface, while pulmonary arterial pressures correlated inversely with flow, ranging from 27/13 to 113/52, expressed as mm. Hg (table 2). The systemic blood flow was below the range of normal only in case 6. Left-to-right shunts of 67 to 24 per cent were calculated in 7 patients and right-to-left shunts of 9 to 31 per cent were found in 5 patients. These shunts were determined from data on blood flow in cases 5 through 8 (table 2); in case 4, the shunt was calculated from indicator-dilution curves after injection of I-1824 into the superior and inferior venae cavae. The evaluation of a right-to-left shunt in this situation is considered in detail later. In 1 instance (case 8), the pulmonary artery was not entered at the time of catheterization, and the wedge pressure in a pulmonary vein was not greatly increased. A considerable gradient existed in case 4 between the right ventricle and the pulmonary artery; pulmonary stenosis was not evident at the time of operation for repair of the atrial anomaly. The agreement between pulmonary venous wedge pressure and pulmonary arterial pressure in cases 1 and 3 may be noted. Comparison of left ventricular and systemic arterial pressures obtained simultaneously or with only a short interval between recordings gave evidence of the amplification of systolic pressure usually seen in the transmission of the pulse wave peripherally.[11] One hour elapsed between records from these sites in case 4, in which this effect was not evident.

Certain noteworthy features are evident in table 2. The left side of the heart or the right pulmonary veins were entered in every patient. This entrance occurred in 5 patients as the catheter was first advanced from the superior vena cava, an unusual event in atrial septal defect of the usual type. The point at which the catheter passed into the lung field was above the bulge of the right atrium in the 7 patients in whom the pulmonary vein was entered (fig. 2*a* and *c*). The catheter passed across the upper part of the cardiac silhouette in the 5 patients in whom the left ventricle was entered (fig. 2*b* and *d*). In 2 instances (cases 3 and 8), considerable difficulty was encountered in passing the catheter from the superior vena cava into the right atrium, the

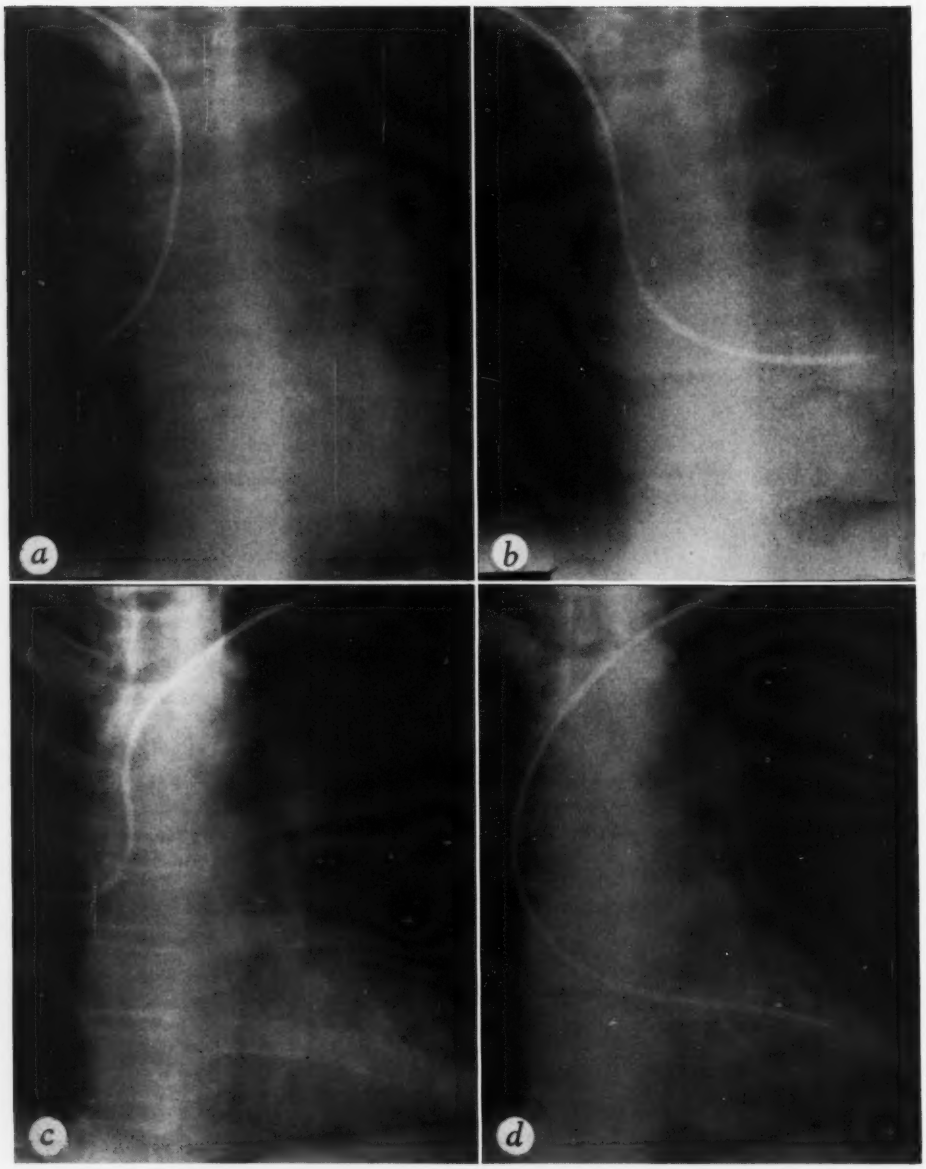


FIG. 2. Roentgenograms obtained at cardiac catheterization: *a* and *b*, from case 3; *c* and *d*, from case 6. The tip of the catheter was in the right superior pulmonary vein (*a* and *c*) and in the left ventricle (*b* and *d*). Note (*a* and *c*) that the catheter entered the pulmonary vein above the main bulge of the right atrial chamber. This high location of the shaft of the catheter makes it extremely unlikely that it traversed an atrial septal defect of the usual type before entering the pulmonary vein.

In *b*, the catheter passes into the left ventricle; although the position of the shaft of the catheter is more cephalad than frequently seen, it could be that of a catheter traversing an atrial septal defect in the usual location (fossa ovalis). The position of the shaft of the catheter in *d* is more typical for that of a catheter entering the left ventricle via an interatrial communication at the fossa ovalis.

tip persistently entering either a pulmonary vein or the left atrium and ventricle.

Oxygen Saturation Values

The oxygen saturation of radial arterial blood was within the range of normal in cases 1, 2, 3, and 5, minimally reduced in cases 4 and 8 and significantly depressed in cases 6 and 7 (table 3). The saturation of pulmonary arterial blood was increased, as is consistent with the presence of the left-to-right shunts, and was always less than that of systemic arterial blood. The saturation of blood from the pulmonary vein was determined by cuvette oximeter in every instance except case 5; however, 2 patients (cases 4 and 7) were breathing 100 per cent oxygen and the values of 100 per cent that were obtained do not indicate the quantity of oxygen present in physical solution. In the remaining cases, the patients were breathing room air and the saturation values of 98 or 99 per cent exceeded the saturation of blood from the radial artery in every instance, although in cases 1, 2, and 3 the saturation of radial arterial blood was within the range of normal.

With regard to the right side of the heart, blood of the highest saturation was obtained from the lower part of the superior vena cava in 6 cases. Samples were not drawn from this region in cases 1 and 2, while in case 8 a sample was not obtained upstream to the site of arterialization in the superior vena cava.

TABLE 3.—*Average Oxygen Saturation of Blood in Great Vessels and Cardiac Chambers in Anomalous Connection of Right Superior Pulmonary Vein*

Case	Blood oxygen saturation, per cent*						
	IVC	MRA	RA-SVC	High SVC	Pulmonary vein	Pulmonary artery	Systemic artery
1	73	87	†	63	99	87	95
2	77	93	†	74	98	86	96
3	‡	87	94	78	98	87	95
4	78	83	90	65	†	82	93
5	81	88	91	79	‡	90	97
6	45	54–60	65	49	99	61	85
7	67	62	72	60	†	68	88
8	66	67	78	†	98	68§	92

* IVC = inferior vena cava; MRA = midportion of right atrium; RA-SVC = right atrial-superior caval junction; SVC = superior vena cava.

† Samples unsuitable or not obtained.

‡ Site not entered at catheterization.

§ Saturation of right ventricular blood; pulmonary artery not entered in this patient.

Indicator-Dilution Curves

The characteristics of indicator-dilution curves obtained after injection of T-1824 into the right and left pulmonary arteries in patients with atrial septal defects and with anomalous pulmonary venous connections have been the subject of a recent report from this laboratory.[12] The dilution curves noted after injection of indicator at these sites in the patients under present consideration showed similar features. Anomalous drainage (left-to-right shunts) of small or moderate magnitude was demonstrated from the left lung, while anomalous drainage of a much greater degree occurred from the right lung. In this respect, these 8 patients were similar to many of those who have atrial septal defects of the more usual type.

Two unusual features in the dilution curves of these patients provided considerable information concerning the pattern of drainage from the right lung in this condition.

1. Preferential Right-to-Left Shunting of Superior as Opposed to Inferior Caval Blood. Small right-to-left shunts from the inferior vena cava are common in patients with atrial septal defects of the usual type, whereas right-to-left shunts from the superior vena cava, when present, are of smaller magnitude.[13] This difference is due to the anatomic relationship of the inferior vena cava to a defect located in the region of the fossa ovalis;[14] subsequent experience has shown conclusively that this is the usual occurrence in patients who have atrial septal defects. In 6 of our 8 patients, indicator-dilution curves were recorded after injection of dye into both the superior and the inferior vena cava, while in the remaining 2 patients (cases 3 and 8), only injections into the superior vena cava were done. In 2 patients (cases 1 and 3), right-to-left shunts were not detected from the superior vena cava (table 4); right-to-left shunts ranging from 5 to 50 per cent were demonstrated in the remainder. In 4 of the 6 patients with injections

TABLE 4.—*Comparison of Circulation Times* and Shunt Values in Anomalous Connection of Right Superior Pulmonary Vein*

Case	Superior vena cava			Inferior vena cava			Right pulmonary vein		
	AT	BT	R-L shunt, per cent	AT	BT	R-shunt, per cent	AT	BT	Normal flow, per cent†
1	9.0	5.0	0	9.0	4.0	0	8.2	5.3	0
2	4.4	2.4	5	6.0	5.0	0	4.8	2.0	6‡
3	7.2	4.5	0	§	§	—	3.3	3.5	63‡
4	4.0	2.8	26‖	6.2	3.8	0	§	§	—
5	5.0	5.0	16	4.0	6.0	26	4.3	5.4	Considerable
6	3.1	3.6	50	5.0	2.3	7	3.2	4.1	67‡
7	7.6	5.4	17	8.0	2.8	9	8.2	6.0	15
8	5.2	3.2	26	§	§	—	4.6	2.8	7

* AT = appearance time (second); BT = build-ups time (seconds).

† Per cent of pulmonary vein blood draining to left atrium.

‡ Curves from pulmonary vein were of methylene blue. In cases 3 and 6, proportion of blood draining normally was calculated thus: $C_{P(pv)}/C_{P(lv)}$, where $C_{P(pv)}$ and $C_{P(lv)}$ refer to the peak concentration after injection into the pulmonary vein and left ventricle, respectively.

§ Not obtained.

‖ This indicates that 9 per cent of the systemic blood flow is represented by shunted blood, since the superior vena cava contributes about one third of the venous return.

into both venae cavae, the right-to-left shunt from the superior vena cava exceeded that from the inferior vena cava (fig. 3). In case 5, a larger right-to-left shunt was demonstrated from the inferior vena cava than from the superior vena cava and, as was predicted, a defect in the region of the foramen ovale was found at operation in addition to the defect situated high in the atrial septum (table 1).

It is apparent that the presence of preferential right-to-left shunting of blood from the superior vena cava is the consequence of the anatomic relation of the superior vena cava to the interatrial communication. The superior free border of the interatrial septum acts as a "dividing crest" to direct a portion of the superior caval blood into the left atrium, just as the limbus of the fossa ovalis acts in regard to inferior caval blood in the usual case of atrial septal defect.

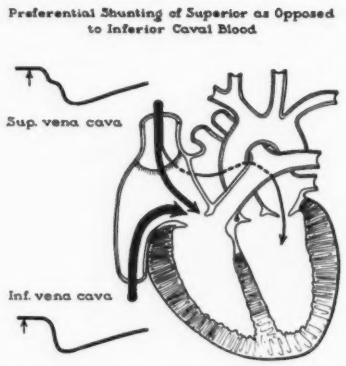


FIG. 3. Diagram of potential flow patterns from superior and inferior venae cavae in anomalous pulmonary venous connection and high atrial septal defect. The solid circles represent sites of injection of indicator. The solid lines indicate direction of passage of dye from the respective sites of injection. The dilution curves (left) are representative of the drainage pattern from each site of injection. Note that the presence of a high interatrial defect permits right-to-left shunting of a small amount of superior caval blood, whereas location of the defect in relation to the inferior vena cava makes occurrence of such a shunt from the inferior vena cava unlikely.

2. Comparison of Dilution Curves Obtained from the Right Pulmonary Vein and from the Superior Vena Cava. The contour of the dilution curve of an indicator is determined largely by the path or paths traversed by the blood from the site of its injection. In deciding whether or not a pulmonary vein entered at cardiac catheterization is anomalously connected, it is of considerable importance to compare the dilution curves obtained after injection of indicator into that vein with the curve recorded after injection of dye into the superior vena cava. Identity or near similarity with regard to appearance time and contour of these curves indicates that the blood from each location drains in the same manner and is strong evidence that a common pathway is traversed by both streams (fig. 4). Conversely, dissimilarity indicates that the blood drains in an essentially different manner and suggests absence of a vascular path common to blood from the pulmonary vein and from the superior vena cava (fig. 5).

Essentially similar dye curves were obtained

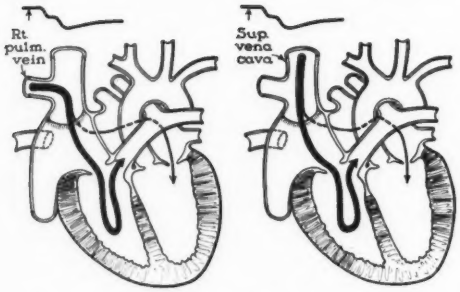


FIG. 4. Demonstration of anomalous drainage of pulmonary vein by identity of dilution curves recorded after injection into anomalously connected pulmonary vein (left) and into superior vena cava (right). Typical dilution curves after injection of indicator are given above the respective diagrams. If the streams of blood share a common pathway for a distance sufficient for mixing to occur, then the drainage pathways of blood from the superior vena cava and the pulmonary vein will be similar, and identical dilution curves will result from injection of indicator at each of these sites. The identical dilution curves after injection of indicator into the superior vena cava and into a pulmonary vein are considered conclusive evidence that the vein is anomalously connected.

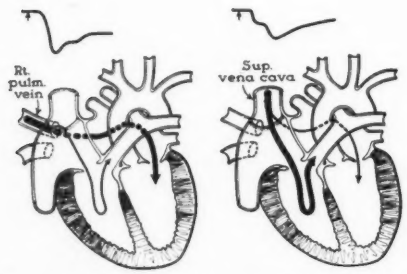


FIG. 5. Different dilution patterns after injection of indicator into the right pulmonary veins and into superior vena cava. When the vein is normally connected to the left atrium (left panel), indicator passes preferentially from this location to the left ventricle and only a small fraction flows from the left atrium into the right atrium. When indicator is injected into the superior vena cava, the dilution pattern is fundamentally different. In this example, a large proportion of right pulmonary vein blood and a small quantity of superior caval blood were considered to pass directly to the left ventricle. These fundamental differences in drainage are seen clearly in the dilution patterns after injection at these sites. Thus, it can be concluded that the pulmonary vein into which the injection of indicator was made is not connected to the superior vena cava.

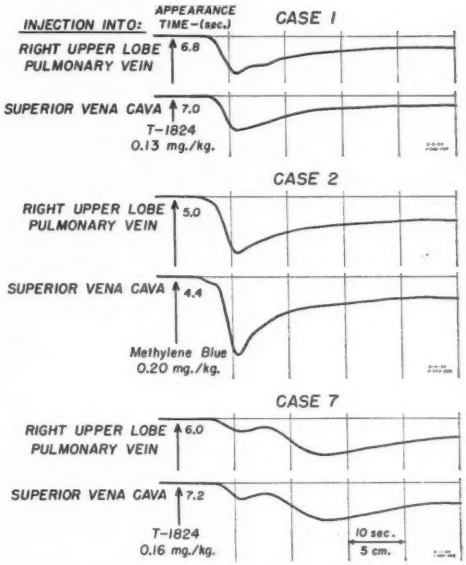


FIG. 6. Demonstration of anomalous drainage of blood from right upper lobe pulmonary veins to superior vena cava in cases 1, 2, and 7. Note in each instance the near identity between the dilution curves obtained after injection at each of these sites, indicating that the vein was anomalously connected in each instance. Note also the absence of a right-to-left shunt of superior caval blood in case 1, the slight degree of shunting in case 2, and the moderate shunt present in case 7.

in cases 1, 2, and 7 (fig. 6) and in case 6 (not shown). Fundamentally dissimilar curves were obtained in cases 3 and 5. A dilution curve from the right pulmonary vein was not obtained in case 4. The magnitude of the right-to-left shunt of superior caval blood was quantitated from the dilution curve.[15] In cases of similar drainage of superior caval and pulmonary venous blood, that portion of the pulmonary venous blood that passes directly to the left atrium is referred to as "normally drained blood," although it circulates in a manner identical to the portion of superior caval blood that is shunted from right to left. Calculation of the "right-to-left shunt" from these curves permits approximate quantitation of the fraction of pulmonary blood draining normally (table 4). In cases 2, 3, 5, and 6, the only indicator injected into the pulmonary vein was methylene blue, whereas T-1824

was used for injection into the superior vena cava. While small right-to-left shunts can be estimated with reasonable accuracy from curves obtained by use of methylene blue, the quantitative evaluation of large shunts by this method may be subject to considerable error, possibly due to loss of this dye in the pulmonary vascular bed. Dilution curves had been obtained in cases 3 and 6 after injection of methylene blue into the left ventricle. In case 5, the catheter did not enter the left ventricle and hence it was not possible to estimate the proportion of pulmonary vein blood draining normally from the pulmonary vein in this patient; however, a large initial deflection resulted from the injection of dye in the pulmonary vein, indicating the presence of normal drainage of considerable magnitude. The dilution curves in case 8 were unusual, indicating that a greater proportion of superior caval blood than of blood from the pulmonary vein passed directly to the left ventricle.

Table 1 shows that a similar anatomic arrangement existed in cases 1, 2, 4, and 6. In case 3, a true anomalous connection was absent. The relation of the anatomic aspects of the lesion to the degree of anomalous drainage demonstrated by the dilution curves is noteworthy.

Discussion

The fact that this report includes 8 patients studied over a relatively short span of time indicates that the association of high interatrial communications with anomalous connection of pulmonary veins to the right atrial-superior vena caval junction is not a rare lesion. The 6 patients operated on were in a group of 90 patients who had interatrial communications and who underwent surgical treatment. An incidence of approximately 10 per cent may represent the frequency of this anomaly among a group of patients presenting the clinical and hemodynamic features of atrial septal defect. This incidence indicates that the anomaly should be sought for diligently, since correction of such a lesion may be difficult or impossible by certain surgical technics.

Repair of atrial septal defects can be accomplished safely by a number of operative procedures. The atrial-well technic now has been used at the clinic in 90 cases for repair of atrial septal defect and left-to-right shunts. To December 1, 1955, this technic had been used in 59 such cases, with 3 deaths.[16] Since then, an additional 31 patients have been operated on, with no deaths. This and other technics allow operation to be done safely in such instances. A persistent common atrioventricular canal should be identified preoperatively, because use of a different procedure, namely extracorporeal circulation, is preferable for such patients. Although the condition of high atrial septal defect and anomalous connection of the right pulmonary veins to the superior vena cava has been repaired successfully by the atrial-well technic and by other procedures, its preoperative identification likewise appears surgically desirable.

These 8 patients presented the clinical features associated with atrial septal defects of the usual type, and distinctive signs that might aid in the differential diagnosis were absent. At cardiac catheterization, passage of the catheter into the pulmonary vein of the right upper or middle lobe from the superior vena cava apparently above the right atrium was an important diagnostic feature. The use of indicator-dilution curves to establish the similarity or dissimilarity of the pattern of drainage from this vein to the pattern from the superior vena cava was a noteworthy feature. Identical drainage patterns were taken as good evidence that the pulmonary vein entered was anomalously connected to the superior vena cava. Dissimilar patterns suggested that the vein was not directly connected to the superior vena cava.

The demonstration that the saturation of blood in the lower part of the superior vena cava or upper part of the right atrium consistently exceeded the values in blood from other parts of the heart strongly pointed to an interatrial communication located high in the atrial septum or an anomalous pulmonary venous connection or both. It has been demonstrated that the proportion of superior caval blood shunted in the right-to-left direction is greater than that of inferior caval blood. In only 1 patient was the right-to-left shunt from

the superior vena cava demonstrated to be of lesser magnitude than that from the inferior vena cava; a defect in the region of the fossa ovalis coexisted in this patient. On the basis of these several findings alone or in combination, the presence of an anomalously connected pulmonary vein was diagnosed before operation in each case. It was soon recognized that this anomalous connection usually was associated with a high interatrial communication, and the significance of preferential right-to-left shunting of superior caval as opposed to inferior caval blood was then apparent. When an anomalous connection of the right pulmonary veins to the superior vena cava accompanies a defect in the region of the fossa ovalis, then preferential shunting of inferior caval as opposed to superior caval blood frequently will suggest the true nature of the anomaly.

Developmental Anatomy

Interatrial communications involving the tissue lying posterosuperior to the region of the fossa ovalis are frequently, if not always, associated with some type of anomaly involving the pulmonary veins. In most of the cases reported in the literature, as well as in those presented in this paper, there is an anomalous connection of the upper right pulmonary veins to the superior vena cava. As a result of the location of the defect, the superior vena cava almost invariably overrides the atrial septum and drains into both atria. In addition to the afore-mentioned 3 certain and 2 probable cases described by Lewis and associates,[1] 16 additional cases have been reported in the literature. Necropsy was done in all these latter cases. Overriding of the atrial septum by the superior vena cava was an obvious feature in many of them. In 1 case of Rokitansky[17] and in a case of Stoeber,[18] cor triatriatum was associated with this type of anomaly. A specimen in the pathologic collection at the clinic furnishes another example of this anomaly associated with cor triatriatum.[19] These last 3 cases are of considerable importance in that they suggest the true nature of the interatrial communication in this malformation. The defect in these 3 cases can be considered correctly as an anomalous connection between the common pulmonary vein and the lowest portion of the superior vena cava. All the components of the true atrial septum, including the septum primum and the septum secundum, had been formed normally. The foramen ovale in each of these cases was valve-competent but patent, opening into the lower chamber of a double left atrium.

The anomalies of the venous system suggested to Edwards and Helmholz[19] that the distinctive type of interatrial communication reported in the present paper can be considered as a persistence of one of the venous connections that normally exist in the fetus between the splanchnic plexus and the cardinal system of veins (fig. 7). By differential growth, the original communication between both systems of veins loses any appreciable length, forming an anomalous connection between the elements originally derived from the pulmonary vein (left atrium or the superior chamber of a cor triatriatum) and the elements derived originally from the adjacent portion of the cardinal system (superior vena cava). Unlike the condition in cor triatriatum, the left pulmonary veins open freely into the left atrium. The process of differential growth that reduces the length of communication between the common pulmonary veins and the superior vena cava allows a shifting of the right pulmonary vein, which now may connect with the superior vena cava in the region of its entry into the right atrium (fig. 8*B* and *C*) or with the posterosuperior wall of the left atrium (fig. 8*A*). In 3 of the patients herein reported (cases 2, 4, and 6), the right superior pulmonary vein drained blood from the upper and middle lobes, whereas in case 5, this vein drained blood from the upper lobe only. The anomalous connection in these patients was of the type depicted in figure 8*C*. Case 3, in which the right pulmonary veins joined to form a small diverticulum of the left atrium, was an example of a connection to the posterosuperior wall of the left atrium (fig. 8*A*), while the anatomic arrangement in case 1 was of the type pictured in figure 8*B*.

Summary

An unusual malformation consisting of anomalous connection of one or more of the

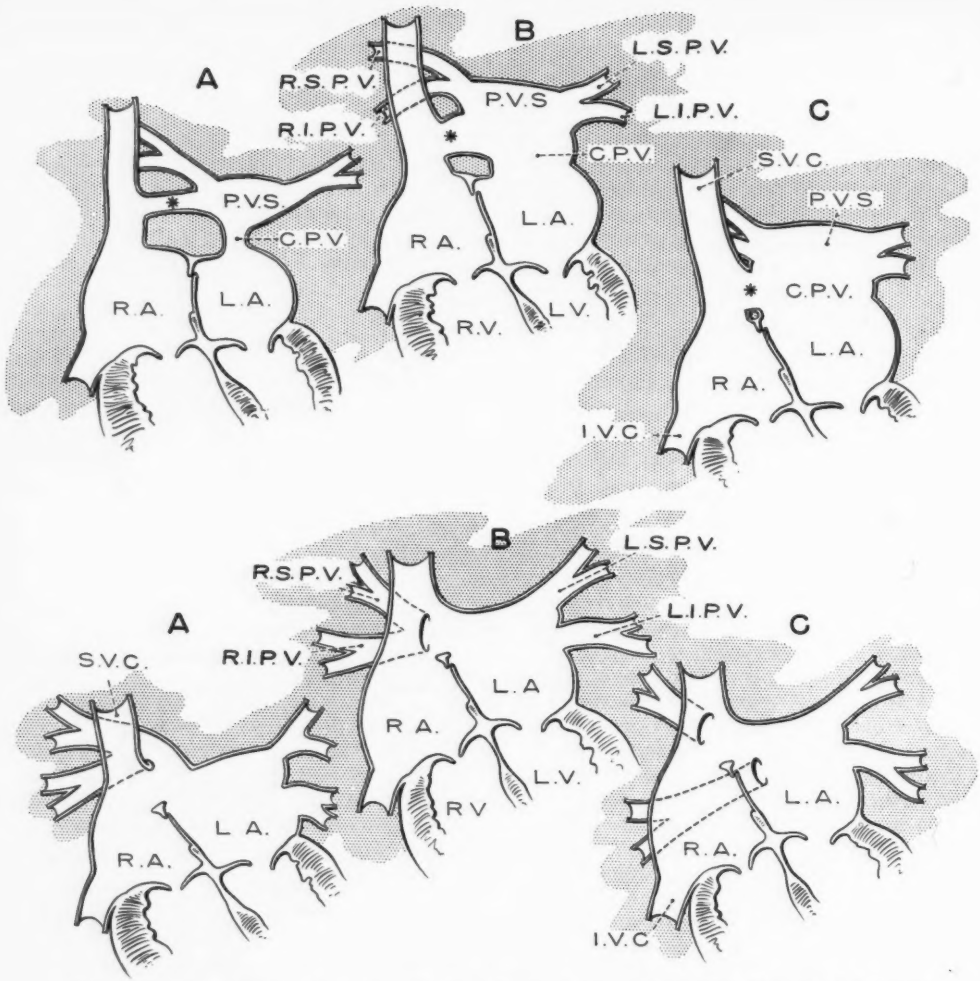


FIG. 7. *Top.* Developmental anatomy of the pulmonary venous sinus (*P.V.S.*), which is formed by union of the right superior (*R.S.P.V.*) and inferior (*R.I.P.V.*) pulmonary veins with the left superior (*L.S.P.V.*) and inferior (*L.I.P.V.*) pulmonary veins, and of the common pulmonary vein (*C.P.V.*). Note persistence of a connection (asterisk) with the primordium of the superior vena cava (*S.V.C.*), as seen in panel A. When the common pulmonary vein is absorbed normally into the left atrium (*L.A.*) and the connection persists, then its relative length is lost and an interatrial communication exists above the fossa ovalis, as shown progressively in panels B and C. This anomaly represents class B, subtype b, in the classification of total anomalous pulmonary venous connection by Edwards and Helmholz.

FIG. 8. *Bottom.* Types of congenital malformation of the heart resulting from persistence of a communication between the pulmonary venous sinus and the primordium of the superior vena cava. *A.* The superior vena cava (*S.V.C.*) straddles the cephalad margin of the atrial septum, in communication with the left atrium (*L.A.*) behind and the right atrium (*R.A.*) in front. The right pulmonary veins join the cephalodorsal portion of the left atrium to form a sinus communicating with the left atrium, the superior vena cava and the right atrium across the cephalad margin of the atrial septum. This anomaly existed in case 3. *B.* The right superior (*R.S.P.V.*) and inferior (*R.I.P.V.*) pulmonary veins connect with the lower portion of the superior vena cava and the upper portion of the right atrium, respectively. Case 1 was an example of this type of malformation. *C.* The right superior pulmonary veins connect to the lower portion of the superior vena cava at the level of the interatrial communication, while the right inferior pulmonary veins connect to the left atrium. This was the commonest variant seen, being present in cases 2, 4, 5, and 6.

right pulmonary veins with the superior vena cava at its junction with the right atrium associated with a high interatrial communication has been diagnosed by means of cardiac catheterization in 8 patients at the Mayo Clinic. In 1 of the 6 patients on whom operation was done, an additional interatrial communication was found in the region of the fossa ovalis. In 4 of the patients, a significant defect in this region was absent. In all 6 patients interatrial communications of moderate size were found localized to the superior aspect of the right atrium close to the entry of the superior vena cava into this chamber. As a result of such location, the superior vena cava overrode the atrial septum in a number of instances. This malformation is believed to be a form of anomalous pulmonary venous connection, in contrast to atrial septal defects of the usual type.

The patients had the symptoms, physical signs, and basic hemodynamic patterns common in atrial septal defect. Features of diagnostic value at cardiac catheterization were as follows:

1. A cardiac catheter could be passed from the superior vena cava into the right pulmonary vein draining the upper or middle lobe from a location above or near the junction of the superior vena cava with the right atrium.

2. The oxygen saturation of samples of blood withdrawn from the juncture of the superior vena cava with the right atrium was equal to or greater than that of other samples from the right side of the heart.

3. There was a preferential right-to-left shunt of the superior caval blood as opposed to inferior caval blood.

4. Anomalous venous drainage of the right upper lobe was demonstrated by the similarity of indicator-dilution curves recorded after injection of dye into the superior vena cava and into the vein and artery of the right upper lobe.

Summario in Interlingua

Catheterisation cardiac de octo patientes al Clinica Mayo resultava in le diagnose de un malformation inusual, consistente del connexion anormal de un o plures del venas dextero-pulmonar con le vena cave superior al puncto de su junction con le atrio dextere, in association con le presentia de un communication alti-interatrial.

Operationes esseva executate in 6 del patientes. In 1 del 6, un communication interatrial additional esseva trovate in le region del fossa oval. In 4 del patientes, nulle defecto significative esseva trovate in iste region. In omne 6 casos, communicationes interatrial de dimensiones moderate esseva trovate localisate al aspecto superior del atrio dextere, proxime al entrata del vena cave superior in iste camera. Como resultato de iste location, le vena cave superior passava in ultra del septo atrial in un numero de casos. Es formulate le opinion que iste malformation es un genere de anormal connexion pulmono-venose, in contrasto con le typo usual de defecto del septo atrial.

Le patientes habeva le symptomas, signos physic, e basic conformation hemodynamic que es le regula in defectos del septo atrial. Observationes de valor diagnostic, facite per catheterisation cardiac, esseva le sequente:

1. Le catheter cardiac poteva esser passate ab le vena cave superior a in le vena dextero-pulmonar, con drainage del lobo superior o medial ab un loco supra o proxime al junction del vena cave superior con le atrio dextere.

2. Le saturation oxygenic de specimens de sanguine obtenite al junction del vena cave superior con le atrio dextere esseva equal o superior al saturation oxygenic de altere specimens obtenite al latere dextere del corde.

3. In le derivation dextero-sinistre le sanguine esseva supero-caval plus tosto que infero-caval.

4. Anormalitate de drainage venose del lobo dextero-superior esseva demonstrate per le similaritate de curvas de dilution de substantia indicatori obtenite post injection del substantia in le vena cave superior con curvas obtenite post injection in le vena e arteria del lobo dextero-superior.

REFERENCES

[1] Lewis, F. J., Taufic, M., Varco, R. L., and Niazi, S.: The surgical anatomy of atrial septal defects: Experiences with repair under direct vision. Ann. Surg. **142:** 401, 1955.

[2] Edwards, J. E.: Pathologic and developmental

considerations in anomalous pulmonary venous connection. Proc. Staff Meet., Mayo Clin. **28:** 441, 1953.

[3] SWAN, H. J. C., BURCHELL, H. B., AND WOOD, E. H.: Differential diagnosis at cardiac catheterization of anomalous pulmonary venous drainage related to atrial septal defects or abnormal venous connections. Proc. Staff Meet., Mayo Clin. **28:** 452, 1953.

[4] BECU, L. M., TAUXE, W. N., DUSHANE, J. W., AND EDWARDS, J. E.: Anomalous connection of pulmonary veins with normal pulmonary venous drainage. Arch. Path. **59:** 463, 1955.

[5] WOOD, E. H.: Special instrumentation problems encountered in physiological research concerning the heart and circulation in man. Science **112:** 707, 1950.

[6] —: Special technics of value in the cardiac catheterization laboratory. Proc. Staff Meet., Mayo Clin. **28:** 58, 1953.

[7] —, LEUSEN, I. R., WARNER, H. R., AND WRIGHT, J. L.: Measurement of pressures in man by cardiac catheters. Circulation Research **2:** 294, 1954.

[8] —: Physical response requirements of pressure transducers for the reproduction of physiological phenomena. Communication and Electronics [Publication of the American Institute of Electrical Engineers]. No. 23, p. 32, 1956.

[9] VAN SLYKE, D. D., AND NEILL, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. I. J. Biol. Chem. **61:** 523, 1924.

[10] NICHOLSON, J. W., III, BURCHELL, H. B., AND WOOD, E. H.: A method for the continuous recording of Evans blue dye curves in arterial blood, and its application to the diagnosis of cardiovascular abnormalities. J. Lab. & Clin. Med. **37:** 353, 1951.

[11] KROEKER, E. J., AND WOOD, E. H.: Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted position in man. Circulation Research **3:** 623, 1955.

[12] SWAN, H. J. C., HETZEL, P. S., BURCHELL, H. B., AND WOOD, E. H.: Relative contribution of blood from each lung to the left-to-right shunt in atrial septal defect: Demonstration by indicator-dilution technics. Circulation **14:** 200, 1956.

[13] —, BURCHELL, H. B., AND WOOD, E. H.: The presence of venoarterial shunts in patients with interatrial communications. Circulation **10:** 705, 1954.

[14] SILVER, A. W., KIRKLIN, J. W., AND WOOD, E. H.: Demonstration of preferential flow of blood from inferior vena cava and from right pulmonary veins through experimental atrial septal defects in dogs. Circulation Research **4:** 413, 1956.

[15] SWAN, H. J. C., ZAPATA-DIAZ, J., AND WOOD, E. H.: Dye dilution curves in cyanotic congenital heart disease. Circulation **8:** 70, 1953.

[16] KIRKLIN, J. W., WEIDMAN, W. H., BURROUGHS, J. T., BURCHELL, H. B., AND WOOD, E. H.: The hemodynamic results of surgical correction of atrial septal defects: A report of thirty-three cases. Circulation **13:** 825, 1956.

[17] ROKITANSKY, C. F. VON: Die Defecte der Scheidewände des Herzens. Vienna, Wilhelm Braumüller, 1875, 156 pp.

[18] STOEBER, H.: Ein weiterer Fall von Cor triatriatum mit eigenartig gekreuzter Mündung der Lungenvenen. Arch. path. Anat. **193:** 252, 1908.

[19] EDWARDS, J. E., AND HELMHOLZ, H. F., JR.: A classification of total anomalous pulmonary venous connection based on developmental considerations. Proc. Staff Meet., Mayo Clin. **31:** 151, 1956.

In the mean time I shall say so much, that there are many things allowed and received in Physiologie, Pathologie, and Medicine, that no body knows the cause of; yet that there are such things no body is ignorant, namely, of rotten feavers, revulsion, purgation of excrement, yet all these things are known by the help of Circulation.—WILLIAM HARVEY, *de Circulatione Sanguinis*, 1649.

Myocardial Sarcoidosis

By ROBERT A. PEACOCK, M.D., EUGENE J. LIPPSCHUTZ, M.D., AND AGNES LUKAS, M.D.

Systemic sarcoidosis frequently involves the heart and is usually diagnosed at autopsy, often as a single granuloma. An extensive review of the literature was prompted by a very interesting clinical problem of etiology in the frequent syncope and Stokes-Adams attacks in an otherwise apparently healthy young girl. The pathologic findings and therapeutic dilemmas are reviewed in detail.

SARCOIDOSIS is generally regarded as a systemic disease of unknown etiology that may involve any organ in a usually benign granulomatous process. In recent years it has become apparent that the myocardium is frequently involved and may result in bizarre arrhythmias or sudden death. This paper presents a review of 28 cases proved by autopsy and adds an additional case manifested by Stokes-Adams attacks.

In table 1 we have listed the cases of myocardial sarcoidosis with autopsy evidence.

The following case presentation (case 29) was puzzling clinically; during the hospital stay virtually every diagnostic and therapeutic test was attempted without success. In retrospect the case was typical of myocardial sarcoid, that is, sudden death in a young individual with a relatively short history of Stokes-Adams attacks.

CASE PRESENTATION

A 27-year-old white woman was admitted June 23, 1955, with a 6-week history of frequent episodes of syncope. An electrocardiogram had revealed the presence of complete heart block. She had been treated unsuccessfully with both sympathomimetic and ganglionic-blocking drugs. The heart rate was reported to vary between 20 and 150. The past history was noncontributory with the exception of albuminuria at the age of 6. She had successfully completed 3 normal pregnancies. A physical examination 15 months previous to admission was normal.

The blood pressure was 110/54 with irregular bradycardia of 28. Temperature was 100 F. rectally and varied between 98 and 100, rising to 101 F. on 3 occasions. Physical examination was entirely normal except for bradycardia and a soft grade II systolic murmur at the apex. Seven complete blood counts and urinalyses were all normal. The sedimentation rate was 8 mm. per hour or less. The fasting blood sugar was 126 mg. per cent, blood urea nitrogen 16 mg., calcium 10.1 mg., phosphorus 4.6 mg., and sodium, potassium, chloride, and CO_2 combining power were all normal. The cephalin flocculation, Wassermann, and Kahn tests were negative. The bromsulfalein retention was 3 per cent. Five blood cultures were sterile. The antistreptolysin titer was 50 units and the C-reactive protein was negative. Agglutinations for *Salmonella typhosa* H and O, *Brucella abortus*, and cold agglutinins were all negative. Complement fixation for Q fever, psittacosis, and lymphogranuloma venereum were all normal. The lupus erythematosus preparation was negative. Skin and muscle biopsies on 2 occasions were reported as showing parimesial reaction only. The electroencephalogram was interpreted as normal. The basal metabolic rate was −25 per cent. Fluoroscopic and radiographic examination of the heart and chest were originally reported within normal limits but on review after autopsy lesions were demonstrable. The esophogram revealed no abnormalities. The electrocardiograms on numerous occasions showed 2:1, 3:1, and complete A-V block.

The patient was given 2.4 mg. of atropine intravenously without effect. She received phenobarbital and also ammonium chloride with no appreciable change. Sodium lactate orally was used in an attempt to raise the pH.[24] A trial of prednisone and large doses of salicylates to the point of toxicity were without effect. Intravenous and repository ACTH for 2 days and 7 days each proved unsuccessful. A trial of thyroid because of the low basal metabolic rate was ineffective.

Numerous syncopal attacks with asystole occurred during the hospital stay. Following a second course of ACTH and 4 weeks without seizures, she was discharged on September 2, 1955.

The patient did well at home until September 24, 1955, at which time she had 2 seizures and was readmitted the next day, in coma. Once again physical examination was not remarkable except for the heart block. An electroencephalogram was again repeated because anoxic changes were feared. The patient did well for 1 day, but on September 27 she suddenly developed complete asystole. Despite intravenous molar lactate and active attempts at

From the Departments of Medicine and Pathology, Buffalo General Hospital and School of Medicine, University of Buffalo, Buffalo, N. Y.

TABLE 1.—*Twenty-nine Cases of Myocardial Sarcoidosis*

	Age, race, and sex	Site of Lesion	Clinical Data	Mode of Death	Reference #
1.	52, W, M	Epicardium	Dyspnea, 2 months	Pneumonia	1
2.	45, W, M	Epicardium	Dyspnea, cor pulmonale on electrocardiogram	Heart failure	2
3.	58, N, F	Myocardium	Dyspnea, heart failure, large heart	Heart failure	3
4.	51, M	Myocardium	Generalized sarcoidosis	Edema of larynx	4
5.	18, N, M	Myocardium and pericardium	Dyspnea, heart failure, tachycardia, complete heart block	Heart failure	5
6.	42, N, M	Myocardium and pericardium	Adams-Stokes syndrome	Suicide	6
7.	40, N, M	Myocardium and pericardium	No symptoms	Sudden death	7
8.	24, N, M	Myocardium	Dyspnea, heart failure, tachycardia, syncope, extrasystoles	Sarcoid	8
9.	27, N, F	Pericardium	Dyspnea, cor pulmonale	Heart failure	9
10.	26, N, M	Myocardium	Angina for 18 months	Sudden death	10
11.	32, N, M	Myocardium	Known sarcoid with tachycardia	Sudden death	11
12.	28, W, M	Myocardium	No symptoms	Suicide	12
13.	25, N, M	Myocardium	Poor vision, tachycardia, ventricular fibrillation	Generalized sarcoid	12
14.	60, W, F	Myocardium	Angina—2 months, paroxysmal atrial tachycardia and flutter	Heart failure	13
15.	29, W, M	Myocardium	No clinical evidence sarcoid No caseation but miliary tubercles in lungs, lymph nodes, etc.	Cerebral hemorrhage	13
16.	26, N, F	Myocardium and epicardium	Palpitation—2 months	Sudden death	14
17.	51, W, M	Myocardium	Dyspnea, heart failure, uveoparotid fever, atrial fibrillation	Heart failure	15
18.	28, N, M	Myocardium	Dyspnea, heart failure, uveoparotid fever, gallop and ventricular tachycardia	Heart failure due to sarcoid	16
19.	50, F	Myocardium	Adams-Stokes, cause unsuspected 15 years	Sudden death	17
20.	28, N, F	Myocardium and pericardium	Dyspnea, cor pulmonale, retinitis, hilar nodes	Heart failure	18
21.	45, W, M	Myocardium and pericardium	Dyspnea, cor pulmonale	Sarcoidosis	19
22.	43, F	Myocardium	Fever with nodes, cough and weakness, 3 months illness	Sudden death	20
23.	20, N, M	Myocardium and pericardium	Dyspnea, congestive heart failure	Shock	21
24.	46, N, M	Myocardium and pericardium	Dyspnea, heart failure, complete heart block, cause unknown	Sudden death	22
25.	27, N, F	Myocardium	Dyspnea, heart failure, cough	Heart failure	22
26.	22, N, F	Myocardium	Ventricular tachycardia, cause unsuspected—hilar nodes	Sudden death	22
27.	45, N, F	Myocardium	Dyspnea, cough, fever, auricular tachycardia	Heart failure	22
28.	54, W, F	Myocardium	Dyspnea, Stokes-Adams, cause unsuspected	Sudden death	23
29.	27, W, F	Myocardium	Stokes-Adams	Sudden death	

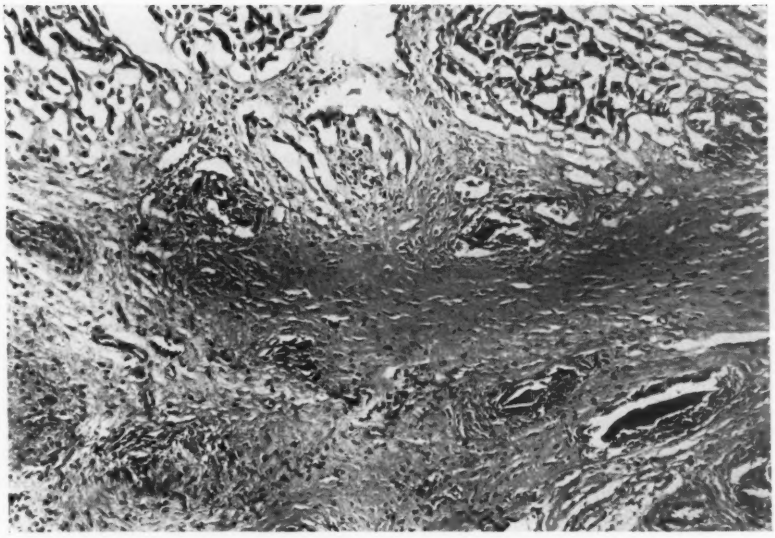


FIG. 1. Heart: Section through the atrioventricular bundle of His, which is completely replaced by sarcoid lesions.

resuscitation, including the use of the cardiac pacemaker, the patient died.

Autopsy Findings

The findings in the heart at autopsy revealed the immediate cause of death. The heart was distinctly enlarged, especially the right ventricle, and to a lesser degree the right atrium, presenting the picture of cor pulmonale with slight hypertrophy of the right ventricular wall and distinct dilatation of the right ventricle. The thickness of the right ventricular wall was 0.6 cm.

The endocardium lining both ventricles was smooth except for an area in the left ventricle just below the right posterior semilunar valve, above the interventricular septum, where the endocardium showed distinctly granular protrusions of slightly yellowish brown color. The clearly noticeable area measured about 1.5 cm. along the heart axis and 1.0 cm. in transverse diameter.

On cut section through this raised area, the underlying myocardium appeared finely nodular. On several cross sections the myocardium was firmer than normal, gray-brown in color, with scattered minute, somewhat yellow nodules. Apart from this finding of the heart, the endocardium, and myocardium appeared entirely normal in both ventricles and atria.

Three sections of the lower part of the membranous septum and through the bundle of His revealed that the endocardium and the underlying muscle bundles were completely replaced by nodular tubercle-like lesions (fig. 1). Serial sections of the area of the atrioventricular node laterally and medially did not show gross or microscopic lesions of sarcoid. Five sections of the interventricular septum and left ventricle showed sarcoid lesions also in the endocardium and subendocardial myocardial muscle fibers. Sections of the ventricular septum and right ventricle were normal. The other 25 sections of the heart taken from the papillary muscles, apex, left ventricle, anterior and posterior wall, and right ventricle were free of sarcoid lesions.

Sections through the above-mentioned granular protrusions showed nodular masses, discrete and confluent tubercle-like lesions, composed of epithelioid cells with Langhans-type giant cells. There was no caseation necrosis and no inflammatory reaction, although there were scattered lymphocytes around the nodules and considerable hyalinization of the endocardium, as well as of the subendocardial tissue.

Special stains for fungi, acid-fast bacilli, and Gram stain were negative.

These histologic findings were typical of sarcoidosis.

The other positive findings were limited to the lungs, lymph nodes, and spleen. The lower lobes of the lungs grossly showed minute, tan-colored granulomatous lesions, largely around the pulmonary arteries. The intrapulmonary lymph nodes were distinctly enlarged and granular. A few granulomatous lesions were found in the upper lobes.

The bronchomediastinal and peritracheal lymph nodes were markedly enlarged and on section, finely granular and gray-white.

The spleen was of normal size, with an irregular surface. On section the spleen was spotted with irregularly outlined granulomatous lesions, yellow-gray and bulging somewhat from the congested parenchyma.

Histologically, all these granulomatous lesions from the lungs, spleen, and lymph nodes were characteristically sarcoid with epithelioid cells and Langhans giant cells. In the lower lobes the intrapulmonary lymph nodes were completely replaced by these nodules. Around the arteries large confluent areas of sarcoidosis showed marked hyalinization in the center.

Discussion

The incidence of sarcoid in the general population is unknown. It is a disease often confused with tuberculosis. Frequently suspected cases fail to be proved by biopsy or autopsy. Freiman[25] estimated 1000 cases reported by 1948. Longcope and Freiman[26] estimated a total of 523 cases of sarcoid reported in this country by 1952. They reviewed 92 cases that had been autopsied and found the heart involved in 20 per cent. However, in a disease that is often without symptoms and in which all evidence of involvement may disappear, it is difficult, if not impossible, to estimate incidence in any postmortem organ clinically. As early as 1938, Pinner, in reporting 18 autopsies, pointed out that 10 of these were unsuspected during life. Ricker and Clark[12] reported 22 cases of which 14 were unsuspected before autopsy. Gilg[19] reported a follow-up study of 191 cases of sarcoid in which there had been 44 deaths; only 10 cases were proved by autopsy and in only 6 was the cause of death directly attributed to sarcoid. The heart was directly involved in only 1 of his cases. It is safe to assume from the statistics presented that sarcoid is a fairly common disease and that in those cases where death has been due to sarcoid, the heart is frequently involved.

The diagnosis of myocardial sarcoidosis has rarely been made during life. Salvesen[27] described a case with tachycardia and heart block in a patient with the skin lesions of sarcoidosis. He attributed the cardiac changes in this patient and in 3 others to sarcoidosis of the myocardium. Bates and Walsh[11] in 1948 attributed ST and T-wave changes to sarcoid of the heart and in 1951 Adickes[16] considered sarcoid as the cause of carditis in 1 patient.

In reviewing the proved cases in the literature, it becomes apparent that when the heart is involved directly by the sarcoid granuloma, the patient often has heart block that may result in sudden death. Of the 29 cases reviewed, 10 terminated in sudden death. Fourteen were described as either Stokes-Adams disease or had clinical features of heart block.

The frequency of tachycardia or other arrhythmias has been pointed out by other authors.[11, 15, 28] In several articles the electrocardiographic changes in cases of suspected myocardial sarcoid have been described.[11, 29]

Reference has been made to the frequency of uveoparotid fever in myocardial sarcoidosis.[5, 26] The duration of clinical sarcoid before death with myocardial involvement has varied from 3 months[20] to 15 years.[17] The majority of the fatal cases are in the third decade (13 out of 29 in table 1).

The diagnosis of myocardial sarcoidosis is most frequently made at autopsy.[12, 26, 30] There was no appreciable sex or racial difference. The transient nature of the cardiac involvement has been pointed out previously[6, 7, 19, 31] and recovery may occur.[7, 21]

Summary

Twenty-nine proved cases of sarcoidosis of the myocardium are reviewed and an additional case is reported. Many additional cases in the literature may be sarcoid of the myocardium. The heart is involved in one fifth of the cases of sarcoid. When death is due to direct involvement of the myocardium, it is likely to be associated with heart block or some other arrhythmia resulting in sudden death.

Summario in Interlingùa

Es presentate un revista de 29 provate casos de sarcoidosis del myocardio. Un caso additional es reportate. Multe altere casos trovate in le litteratura es possibilemente etiam sarcoide del myocardio. Le corde es afficite in un quinto del casos de sarcoide. Quando le morte resulta directemente del affection del myocardio, illo occurre con alte grados de probabilitate subitemente e in association con bloco cardiac o un altere arrhythmia.

REFERENCES

[1] Bernstein, M., Konzlemann, F. W., and Sidlick, D. M.: Boeck's sarcoid. A report of a case with visceral involvement. Arch. Int. Med. **44:** 721, 1929.

[2] Schaumann, J.: Lymphogranulomatosis benigna in the light of prolonged clinical observations and autopsy findings. Brit. J. Derm. **48:** 399, 1936.

[3] Nickerson, S. A.: Boeck's sarcoid: Report of 6 cases in which autopsies were made. Arch. Path. **24:** 19, 1937.

[4] Spencer, J., and Warren, S.: Boeck's sarcoid: Report of a case with clinical diagnosis confirmed at autopsy. Arch. Int. Med. **62:** 285, 1938.

[5] Cotter, E. F.: Boeck's sarcoid. Autopsy in a case with visceral lesions. Arch. Int. Med. **64:** 286, 1939.

[6] Longcope, W. T., and Fisher, A. M.: The effect of Schaumann's disease upon the heart and its mechanisms. Acta med. Scandinav. **108:** 529, 1941.

[7] —, and —: Involvement of the heart in sarcoidosis or Besnier-Boeck-Schaumann disease. J. Mt. Sinai Hosp. **8:** 784, 1942.

[8] Johnson, J. B., and Jason, R. S.: Sarcoidosis of the heart. Am. Heart J. **27:** 246, 1944.

[9] Hauser, J.: Pulmonary sarcoidosis. J. Oklahoma M. A. **39:** 395, 1946.

[10] Scotti, T. M., and McKeown, C. E.: Sarcoidosis involving the heart: Report of a case with sudden death. Arch. Path. **46:** 289, 1948.

[11] Bates, C. S., and Walsh, J. M.: Boeck's sarcoid: Observations on 7 patients, 1 autopsy. Ann. Int. Med. **29:** 306, 1948.

[12] Ricker, W., and Clark, M.: Sarcoidosis, a clinicopathologic review of 300 cases including 22 autopsies. Am. J. Clin. Path. **19:** 725, 1949.

[13] Voght, H.: Besnier-Boeck-Schaumann disease. Helvet med. acta, suppl. **22:** 1, 1949.

[14] Kulka, W. E.: Sarcoidosis of the heart. A cause of sudden and unexpected death. Circulation **1:** 772, 1950.

[15] Yesner, R., and Silver, M.: Fatal myocardial sarcoidosis. Am. Heart J. **41:** 777, 1951.

[16] Adickes, G. C., Zimmerman, S. L., and Cardwell, E. S., Jr.: Sarcoidosis with fatal cardiac involvement. Ann. Int. Med. **35:** 898, 1951.

[17] Simpkins, S.: Sarcoid with complete heart block. J.A.M.A. **146:** 794, 1951.

[18] Gendel, B. R., Young, J. M., and Greiner, D. J.: Sarcoidosis. Review with 24 additional cases. Am. J. Med. **12:** 205, 1952.

[19] Gilg, I.: Sarcoidosis involving the heart. Acta dermat.-venereol. **33:** 318, 1953.

[20] Oille, W. A., Ritchie, R. C., and Barrie, H. J.: The age of the lesions in a case of myocardial sarcoidosis. Canad. M.A.J. **68:** 277, 1953.

[21] Sales, L. M.: Sarcoidosis of the myocardium: Report of a case. J. Florida M. A. **40:** 27, 1953.

[22] Powell, L. W.: Sarcoidosis of the myocardium. North Carolina M. J. **15:** 28, 1954.

[23] Gottfarb, G., and Wahlgren, F.: Adams-Stokes Syndrome framkallat av morbus Besnier-Boeck-Schaumann. Nord. med. **52:** 985, 1954.

[24] Bellet, S., Wasserman, F., and Brody, J. I.: Treatment of cardiac arrest. Circulation **11:** 685, 1955.

[25] Freiman, D. G.: Sarcoidosis. New England J. Med. **239:** 664, 709, 743, 1948.

[26] Longcope, W. T., and Freiman, D. G.: A study of sarcoidosis: Based on a combined investigation of 160 cases including 30 autopsies from the Johns Hopkins Hospital and the Massachusetts General Hospital. Medicine **31:** 1, 1952.

[27] Salvesen, H. A.: The sarcoid of Boeck: A disease of importance to internal medicine. Report on 4 cases. Acta med. Scandinav. **86:** 127, 1935.

[28] Riley, E. A.: Boeck's sarcoid: A review based upon clinical study of 52 cases. Am. Rev. Tuberc. **62:** 231, 1950.

[29] Leitner, St. J.: Elektrokardiographische und spirometrische Untersuchungen bei Epitheloidzelligen Granulomatose. Cardiologia **10:** 379, 1946.

[30] Weeden, W. F., and Beckh, W.: Sarcoidosis: A review of 34 cases. Stanford M. Bull. **10:** 39, 1952.

[31] Moyer, J. H., and Ackerman, A. J.: Sarcoidosis: A clinical and roentgenological study of 28 cases. Am. Rev. Tuberc. **61:** 299, 1950.

The subtlety of nature is greater many times over than the subtlety of the senses and understanding; so that all those pretty meditations, speculations, and controversies in which men indulge are really quite mad, only there is no one detached enough to observe it.—Bacon, 1561–1626.

Effect of Protamine on Alimentary Lipemia

By Allan J. Day, M.B., M.Sc., Gwendoline K. Wilkinson, M.Sc., Hugh R. Gilmore, M.B., M.R.A.C.P., M.R.C.P., and Colin J. Schwartz, M.B.

With the technical assistance of J. A. Peters, D.M.T.

The effect of protamine on the serum lipids during alimentary lipemia was investigated in normal male students and this effect was compared with that in atherosclerotic and in nonatherosclerotic men of the same age group. In the student group protamine produced a highly significant increase in the total fatty acid level, whereas in the 2 older groups no significant change occurred. These results were interpreted as demonstrating that circulating heparin exerts a physiologic effect on fat turnover in the young individual, an effect that is reduced with aging. It is suggested that the lowered fat tolerance known to occur with aging is the result of deficiency of circulating heparin.

SINCE Hahn[1] reported in 1943, that heparin reduced alimentary lipemia, a considerable volume of work has been done in an attempt to define the mechanism of this effect. In addition, the physiologic role of circulating heparin in lipid transport has been investigated. One line of approach has been the investigation of the effect of antiheparin substances such as protamine on the serum lipids. These substances have recently been shown to cause a rise in plasma lipid and lipoprotein levels in experimental animals under a variety of circumstances.[2-5] In this present work the effect of protamine on serum lipids following fat ingestion in human subjects has been investigated. Further, since there is evidence that atherosclerosis may be associated with a disturbance in normally occurring blood heparinoids[6] or in the response of lipids to them,[7, 8] the effect of protamine on the blood lipids of atherosclerotic patients was determined and the response compared with that of control subjects. While this work was in progress, Moeller and co-workers[9] reported that protamine caused an elevation in total fatty acids and in visible lipemia following the ingestion of fat in normal subjects. Our results confirm these findings and in addition demonstrate the differing response to protamine of a group of young individuals to that of atherosclerotic and nonatherosclerotic individuals of the same age group.

From the Department of Human Physiology and Pharmacology and the Department of Medicine, University of Adelaide, South Australia.

This work was aided by a grant from the National Health and Medical Research Council of Australia.

Methods

Three groups with 9 individuals in each were investigated. The first group consisted of normal male medical students with ages varying from 19 to 35 years (average 25 years). The second group were atherosclerotic patients with a hospital record of myocardial infarction 3 to 12 months prior to the experiment; their ages varied from 40 to 68 years (average 58 years). The third group were nonatherosclerotic men of approximately the same age as the atherosclerotic subjects (43 to 64 years, average 51 years). They were hospital patients with no evidence of atherosclerosis as judged by a clinical assessment of the cardiovascular system, a normal blood pressure, and a normal electrocardiogram. These patients were convalescing from conditions without any recognizable bearing on fat absorption or its metabolism.

The procedure in each individual was as follows: the subject was fasted overnight and then given a standard fat meal consisting of 100 ml. of cream with cocoa and sugar to taste. Blood samples were taken in the fasting state and then at 135 and 150 minutes after the fat meal. Immediately following the 150-minute sample, an intravenous injection of 100 mg. of protamine sulfate was administered. Two further blood samples were taken at 15-minute intervals after the injection, i.e., at 165 and 180 minutes. The 5 samples were designated O, A, B, C, and D. Serum total esterified fatty acids, serum cholesterol, serum phospholipid, and the visible lipemia were determined in each sample. To provide control measurements for the assessment of protamine effect the procedure was repeated using 10 ml. of saline instead of protamine.

The student group was also used a third time, but 5,000 units of heparin were given intravenously instead of protamine.

Chemical Determinations. Serum total esterified fatty acids were determined by the method of Stern and Shapiro,[10] serum cholesterol by the method of Zlatkis, Zak, and Boyle,[11] and serum

phospholipids by the method of Brown.[12] These methods were modified in this laboratory as described in a previous communication.[5]

Visible lipemia was determined by directly reading optical density at a wave length of 650 mμ. in a Unicam S.P. 600 spectrophotometer with a 1-cm. cuvette. The serum was diluted prior to reading with 2½ times its volume of a 20 per cent urea solution.

Results

The response to protamine in the serum lipid fractions was measured for each individual by comparing the rise in serum lipids after the injection of protamine, with the rise after the injection of saline.

Protamine effect

$$= \frac{(C+D)-(A+B)}{2}_{\text{Protamine}} - \frac{(C+D)-(A+B)}{2}_{\text{Saline}}$$

where A and B are the 2 samples taken before the injection, and C and D are the 2 samples following it.

Table 1 gives the mean response to protamine in the total fatty acids, cholesterol, phospholipids, and visible lipemia for each of the groups, together with the estimated standard errors of the means. Analyses of variance (not presented) showed that the groups differed significantly only in their response in the total fatty acid levels to the protamine injection. There was a significant over-all response to protamine in cholesterol and visible lipemia, but this was of the same magnitude for all 3 groups. The phospholipid levels showed no significant changes in any of the groups studied.

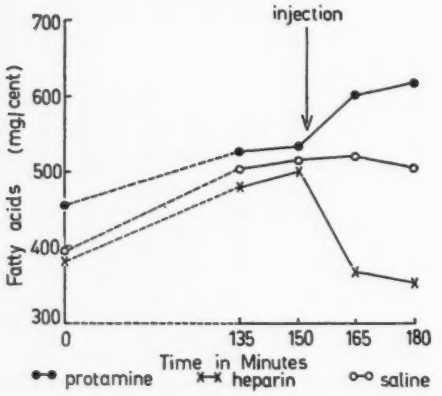
With regard to the fatty acids, the student group showed a large response to the protamine injection, 73 ± 19 mg. per cent, which was as great as the rise already induced by the ingestion of the fat meal 2½ hours earlier. Figure 1 illustrates the rise following the protamine injection and compares it with the normal fat curve, which showed no response to the saline. The striking response to protamine in the student group contrasted with that in the atherosclerotic group and in the group of non-atherosclerotic controls of the same age range, where the mean responses were much smaller and not significant. Figures 2 and 3 illustrate the similarity of the curves in these 2 older groups, following either protamine or saline injections. The shape of the fat tolerance curves were essentially similar, but differed from that of the younger student group. A comparison of the "saline curve" of figures 1, 2, and 3 shows that after 3 hours the total fatty acid level of the student group was falling, whereas in the older groups the levels continued to rise over the whole period of the experiment.

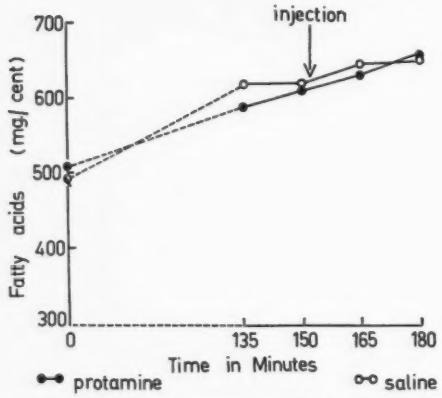
The effect of heparin on the level of the total fatty acids of the student group is shown also in figure 1. Compared with the saline injection, heparin caused a reduction of 134 ± 23 mg. per cent, a change that is highly significant ($p < 0.001$). No significant response to heparin was found in the serum cholesterol and phos-

Table 1.—*Effect of Protamine on Serum Lipids*

		Students	Atherosclerotic	Elderly control	Groups combined
Fatty acids	Mean diff.	72.61 (9)*‡	14.33 (9)	9.83 (9)	32.26 (27)
	S.E. of mean	19.38 (8)†	17.53 (8)	15.23 (8)	10.08 (24)
Cholesterol	Mean diff.	15.33 (9)	8.33 (9)	7.00 (9)	10.22 (27)‡
	S.E. of mean	6.94 (8)	2.80 (8)	6.24 (8)	3.25 (24)
Phospholipids	Mean diff.	6.89 (9)	−3.44 (9)	3.78 (9)	2.41 (27)
	S.E. of mean	7.11 (8)	4.90 (8)	7.62 (8)	3.80 (24)
Visible lipemia	Mean diff.	0.0188 (9)	0.0345 (8)	0.0323 (9)	0.0283 (26)§
	S.E. of mean	0.0112 (8)	0.0098 (7)	0.0077 (8)	0.0056 (23)

* N.
† Degrees of freedom.
‡ Significant at 1 per cent level (by t test).
§ Significant at 0.1 per cent level (by t test).





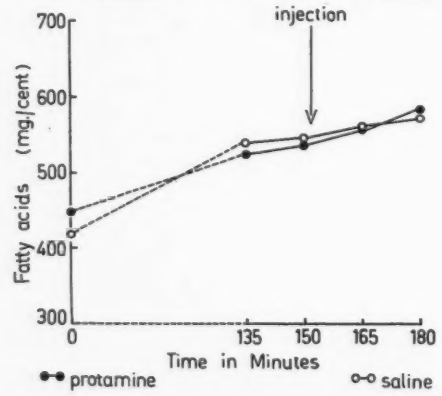


FIG. 1. *Top*. The effect of heparin, protamine, and saline on the total fatty acids of normal students following the ingestion of fat.

FIG. 2. *Middle*. The effect of saline and of protamine on the total fatty acids of atherosclerotic subjects following the ingestion of fat.

FIG. 3. *Bottom*. The effect of saline and of protamine on the total fatty acids of nonatherosclerotic subjects following the ingestion of fat.

pholipid levels, the rise being 4.3 ± 3.0 mg. per cent and 4.8 ± 3.8 mg. per cent respectively.

DISCUSSION

Protamine has been shown to produce a highly significant increase in the total fatty acids of students during alimentary lipemia, but to have no effect on patients in the older age groups irrespective of the presence or absence of atherosclerosis. The striking effect of protamine in the student group can most readily be explained on the basis of its opposing the physiologic action of heparin in fat transport; most workers who have shown lipid changes with protamine accept this viewpoint of its action. The observation also recorded in this work that heparin itself reduces total fatty acids during alimentary lipemia serves to highlight this interpretation. Spitzer,[3] however, in view of his failure to obtain results with other antiheparin drugs and because of the relatively long latent period before the effect of protamine is manifested, suggested that the effect of protamine on lipemia is a "*sui generis* action," and not due to its antiheparin effect. Against this view are the findings of other workers[4, 5, 13] who obtained lipid changes with other antiheparin drugs. Further, it is to be expected that protamine will have a delayed effect on lipids if it is antagonizing heparin. If one envisages heparin dealing with lipid entering the circulation from the alimentary tract, the sudden elimination of this heparin will not have any immediate effect on the blood lipids. Subsequently, however, with progressive absorption of more fat, it will not be dealt with adequately and the level will rise.

If one accepts the view that the action of protamine is due to its opposing circulating heparin, it follows that the failure to produce significant changes in fatty acids in the 2 groups of older individuals can be attributed to a deficiency of heparin in these persons. We conclude that this decrease in circulating heparin is a feature of advancing years. The observations of Hellström and Holmgren[14] of a marked decrease with advancing age of heparin-producing mast cells would fit well with this concept. Further, the low fat tolerance known

to be present in older subjects[15, 16] may be similarly explained. This tendency to low fat tolerance is seen in this present work when the "saline curves" for fatty acids of the 3 groups are compared. It is reasonable to conclude that this lowered fat tolerance is due to a reduced level of heparin in these subjects, with the result that fat entering from the alimentary tract is not dealt with adequately. It is possible in this regard to draw a rough analogy between the blood glucose level and insulin on the one hand, and circulating fat and heparin on the other.

The object of this work has been to determine the significance of a possible "heparin deficiency" in the pathogenesis of atheroma. On the evidence presented, however, the conclusion is that there is a deficiency of heparin with advancing age. This deficiency may represent a phenomenon that characterizes aging in the human individual, and is not necessarily related to the incidence of atherosclerosis. The difficulty of excluding atherosclerosis by clinical assessment is fully appreciated, and it is possible that unsuspected atheroma was present in the individuals thought to be free of this condition, and who were of a similar age to the cases of proved atherosclerosis.

It is worth noting in this regard that many workers who have investigated lowered fat tolerance in atheroma,[16, 17] and the effect of heparin on serum lipids in atherosclerotic individuals[7] have used younger individuals as controls. It is therefore impossible to know whether their results were determined by age or by atheroma.

Summary

The intravenous administration of 5,000 units of heparin produced a highly significant reduction in the serum total fatty acids in a group of normal students following the ingestion of a fat meal. No changes in the serum cholesterol or phospholipids were recorded.

The administration of 100 mg. of protamine sulfate under similar circumstances, to the same group of subjects, caused a highly significant elevation in the total fatty acids. Protamine had no significant effect on the total fatty acids of a group of atherosclerotic subjects or on a similar age group of nonatherosclerotic subjects. Protamine significantly elevated the serum cholesterol and the visible lipemia of the 3 groups studied, but no difference could be detected among the 3 groups in these measurements. No effect of protamine on the phospholipids was found in any of the groups investigated.

Summario in Interlingua

Le administration intravenose de 5.000 unitates de heparina produceva un altemente significative reduction del total acidos grasse del sero in un gruppo de studentes normal post le ingestion de un repasto ric in grassia. Esseva notate nulle alterationes in le sero quanto al contento de cholesterol o de phospholipidos.

Le administration de 100 mg de sulfato de protamina al mesme gruppo de subjectos e sub le mesme conditiones causava un altemente significative elevation del total acidos grasse. Protamina habeva nulle effecto significative super le total acidos grasse de un gruppo de subjectos atherosclerotic e de un gruppo de subjectos non-atherosclerotic de simile etates. Protamina causava in omne le tres gruppos studiate un elevation significative del cholesterol seral e del lipemia visibile. sed nulle differentias esseva notate inter le mesurationes pro le gruppos individual. Nulle effecto de protamina super le phospholipidos esseva trovate in ulle del gruppos studiate.

Acknowledgment

We are indebted to Dr. W. D. Brown of the Department of Biochemistry for advice and encouragement and to Mr. G. N. Wilkinson of the Division of Mathematical Statistics, Commonwealth Scientific and Industrial Research Organisation, for the statistical evaluation of the results. We are also grateful to the students and patients who cooperated in this investigation.

REFERENCES

1 Hahn, P. F.: Abolishment of alimentary lipemia following injection of heparin. Science **98:** 19, 1943.

2 Brown, W. D.: Reversible effects of anticoagulants and protamine on alimentary lipemia. Quart. J. Exper. Physiol. **37:** 75, 1952.

3 Spitzer, J. J.: The influence of protamine on alimentary lipemia. Am. J. Physiol. **174:** 43, 1953.

[4] Bragdon, J. H., and Havel, R. J.: In vivo effect of anti-heparin agents on serum lipids and lipoproteins. Am. J. Physiol. **177:** 128, 1954.

[5] Day, A. J., Wilkinson, G. K., and Schwartz, C. J.: The effect of toluidine blue on serum lipids and lipoproteins in rabbits. Australian J. Exper. Biol. **34:** 415, 1956.

[6] Nikkilä, E. A., and Majanen, S.: The blood heparinoid substances in human atherosclerosis. Scandinav. J. Clin. & Lab. Invest. **4:** 204, 1952.

[7] Block, W. J., Barker, N. W., and Mann, F. D.: Effect of small doses of heparin in increasing the translucence of plasma during alimentary lipemia: studies in normal persons and patients having atherosclerosis. Circulation **4:** 674, 1951.

[8] Oliver, M. F., and Boyd, G. S.: The clearing by heparin of alimentary lipemia in coronary artery disease. Clin. Sc. **12:** 293, 1953.

[9] Moeller, H. C., Bernstein, L. M., Palm, L., and Grossman, M. I.: The effect of protamine on lipemia. J. Lab. & Clin. Med. **47:** 270, 1956.

[10] Stern, I., and Shapiro, B.: A rapid and simple method for the determination of esterified fatty acids and for total fatty acids in blood. J. Clin. Path. **6:** 158, 1953.

[11] Zlatkis, A., Zak, B., and Boyle, A. J.: A new method for the direct determination of serum cholesterol. J. Lab. & Clin. Med. **41:** 486, 1953.

[12] Brown, W. D.: Determination of lipid phosphorus in ultramicro quantities of serum. Australian J. Exper. Biol. **32:** 677, 1954.

[13] Hewitt, J. E., Hayes, T. L., Gofman, J. W., Jones, H. B., and Pierce, F. T.: Effects of total body irradiation upon lipoprotein metabolism. Am. J. Physiol. **172:** 579, 1953.

[14] Hellström, B., and Holmgren, H.: En Kvantitativ analys av masteellförekomstem i hud och hjärta hos manniska. Svenska läk.—sällak. forhandl. **44:** 617, 1947.

[15] Becker, G. H., Meyer, J., and Necheles, H.: Fat absorption and atherosclerosis. Science **110:** 529, 1949.

[16] Pomeranze, J., and Bienfield, W. H.: Fat tolerance relationship to atherosclerosis. Bull. New York M. Coll. **14:** 70, 1951.

[17] Woldow, A., Chapman, J. E., and Evans, J. M.: Fat tolerance in subjects with atherosclerosis: heparin effects upon lipemia, lipoproteins and gamma globulin. Am. Heart J. **47:** 568, 1954.

Stuckey, D.: Congenital Heart Defects Following Maternal Rubella during Pregnancy. Brit. Heart J. **18:** 519 (Oct.), 1956.

Of 426 patients with congenital heart disease seen during a 5-year period, 27 presented with a history of maternal rubella, 13 had patent ductus arteriosus, 4 ventricular septal defect, 3 atrial septal defect, 2 Fallot's tetralogy, and 1 each suffered from aortic stenosis, pulmonary stenosis, coarctation of the aorta, the Eisenmenger's complex, and transposition of the great vessels. One fourth to one third of those with patent ductus arteriosus had an additional cardiac lesion. Deafness, cataract, or both occurred in 9 with patent ductus arteriosus and in 3 with atrial septal defect. The incidence of patent ductus arteriosus in children born of mothers who had suffered from rubella during pregnancy was about 88 times and that of other congenital heart lesions was 11 times the normal incidence. The higher incidence of patent ductus arteriosus may be due to its longer normal duration in the fetus.

Soloff

Cardioaortic Fistula

Temporary Circulatory Occlusion as an Aid in Diagnosis

By BERNARD L. BROFMAN, M.D., AND JOHN C. ELDER, M.D.

Rupture of a sinus of Valsalva aneurysm into the right ventricle produces a dramatic clinical syndrome characterized by a rapid and relentlessly unfavorable course. Early diagnosis is essential for surgical repair before an irreversible stage is reached. Cardiac catheterization and retrograde aortography confirmed the diagnosis in the case reported. With the aid of temporary circulatory occlusion, the fistula was demonstrated by contrast material injected via an aortic catheter. Although the fistula and the accompanying ventricular septal defect were closed at open-heart surgery, the markedly enlarged heart could not resume its function.

SUDDEN rupture of an aneurysm of a sinus of Valsalva into a low pressure chamber of the heart has always been considered a medical curiosity and of only academic interest. Only rarely has a definitive diagnosis been made prior to exploratory operation or autopsy.[1-5] Unruptured congenital aneurysms of the sinuses of Valsalva are probably not too rare[6] and have been demonstrated in life by angiocardiography;[7, 8] they are presumably of little hemodynamic significance. However, once rupture occurs, a medical emergency exists. This catastrophe always results in rapid circulatory deterioration, with death supervening within a period ranging from a few days to several years. Recent advances in intracardiac surgery render such a condition amenable to surgical correction. The diagnosis must be established soon after rupture occurs, otherwise the relentless deteriorating course may well preclude later diagnostic and therapeutic measures.

The clinical picture appears to be so typical that the diagnosis should be suspected without special studies. However, an absolute diagnosis can be established only by demonstrating the shunt, with the aid of suitable technics. In the case presented here the clinical picture was correctly interpreted as that of rupture of a sinus of Valsalva into the right ventricle. The special studies were, of course, confirmatory, and demonstrated the exact localization of the lesion, thus determining the surgical approach.

The actual demonstration of the fistula was accomplished with the aid of a new diagnostic technic devised to meet the immediate needs of this case. *Temporary circulatory occlusion* reduced circulation to the degree that the retrograde injection of contrast material into the aorta demonstrated the fistula from the right sinus of Valsalva into the right ventricle.

Operation was carried out with the aid of an artificial heart-lung apparatus. Unfortunately, the markedly dilated and hypertrophied heart fibrillated even before the machine had taken over the circulation. The lesion was repaired as planned. However, even with successful repair, irreversible failure precluded recovery.

CASE REPORT

A 26-year-old white man was known to had have a heart murmur since childhood. There was no history of rheumatic fever or other serious childhood disease. He had been completely asymptomatic with no limitation of activity until June 1955, at which time he suddenly developed easy fatigability and dyspnea on slight exertion. There was no undue exertion or chest pain associated with the onset of symptoms. It was reported that there was a marked change in the heart murmur at that time. Orthopnea and pedal edema appeared within a few days of the onset of symptoms and became rapidly worse. He was placed on strict bed rest, digitalis, and frequent mercurial diuretics with rather striking improvement, and he was able to return to a sedentary job within a few weeks. However, in December 1955, his symptoms had progressed to the point where he was completely incapacitated, the slightest activity causing severe dyspnea.

From the Eva and Irving Hexter Laboratory for Cardiovascular Research, Mount Sinai Hospital, Cleveland, Ohio.

This work was aided by Grants from the Cleveland Area Heart Society.

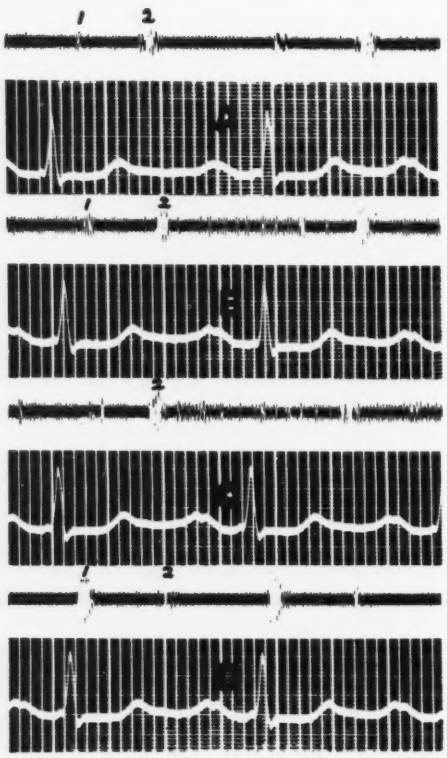


FIG. 1. Phonocardiograms in patient with cardioaortic fistula. *A*. Aortic area. *B*. Pulmonic area. *C*. Third left intercostal space, 5 cm. from midsternal line. Continuous murmur heard best at this position. *D*. Apex.

He was first hospitalized in February, 1956. At this time he did not appear to be in acute distress, but was obviously chronically ill. The skin appeared to have a slightly cyanotic tinge. The peripheral arterial pulses were bounding; the brachial artery pressure (by sphygmomanometer) was 140 systolic; the diastolic pressure was usually read as 50 to 60 although muffled sounds could be heard to 0. The heart was markedly enlarged; the apex beat was at the anterior axillary line in the sixth intercostal space.

The heart sounds were of normal intensity except for accentuation of the pulmonic second sound. There was a very loud harsh continuous machinery-like murmur heard best in the third left intercostal space 5 cm. from the midsternum. The murmur was widely transmitted over the precordium (fig. 1). A readily palpable continuous thrill was also present. The lungs showed occasional basilar rales. The liver was palpable 2 cm. below the costal margin. Urine and blood studies were essentially normal.

Cardiac fluoroscopy revealed a markedly enlarged heart, with generalized chamber enlargement (fig. 2). The pulmonary artery was prominent with increased pulsations; the aortic knob was small. The electrocardiogram showed combined ventricular hypertrophy.

The abrupt onset together with the clinical findings suggested the diagnosis of rupture of a sinus of Valsalva into the heart. Cardiac catheterization was carried out, followed by angiocardiography.

The patient was then discharged, to return for definitive surgery. During this period he remained at home, on digitalis, receiving weekly mercurial injections with no progression of his symptoms. He was readmitted in August 1956, at which time the final angiographic studies were carried out and open-heart surgery was eventually performed.

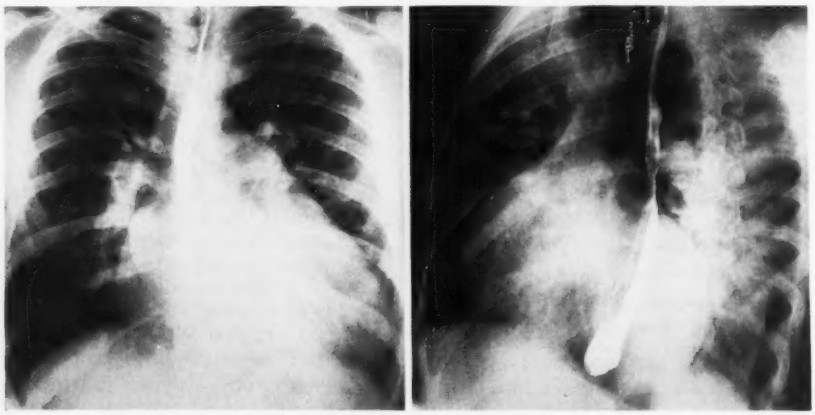


FIG. 2. X-rays of the heart, demonstrating generalized chamber enlargement; *P.A.* and left anterior oblique views shown. The pulmonary artery and left ventricle are prominent, with a small aortic knob.

Hemodynamic Studies

Cardiac catheterization was performed using a special triple-lumen catheter with an inflatable cuff. This type of catheter has been used in this laboratory to produce unilateral pulmonary artery occlusion and in determination of the size of intracardiac defects.[9] Simultaneous samplings in adjacent chambers were obtained via the different lumens. The catheter readily entered a markedly dilated right atrium, but there was considerable difficulty in manipulating it into the right ventricle and then into the pulmonary artery. Pressures were recorded via electromanometers and a Sanborn Polyviso. Duplicate blood samples for determinations of oxygen content were obtained from the various chambers.

Percutaneous insertion of a plastic catheter into the left femoral artery permitted arterial blood sampling and pressure recording. Oxygen consumption was determined by means of a Collins respirometer.

The pulmonary "capillary" (wedge) pressure could not be obtained in the usual manner. In order to do so, the right pulmonary artery was occluded temporarily by inflating the cuff with 10 ml. of contrast material. Distal to occlusion, the pressure and blood oxygen content were obtained. These are considered equivalent to "pulmonary capillary" determinations.[9]

Table 1.—*Hemodynamic Data*

	Pressure (mm. Hg)	O_2 content (vol.%)
Superior vena cava	18/10	9.7
High right atrium	18/10	10.6
Low right atrium	18/10	11.5
Right ventricular inflow	65/14/18 (mean 28)	13.9
Right ventricular outflow	65/14/18 (mean 28)	16.4
Main pulmonary artery	60/28 (mean 38)	15.1
Left pulmonary artery	60/28 (mean 38)	15.0
Right pulmonary artery	60/28 (mean 38)	15.0
"Pulmonary capillary"	20/10	17.0 (91%)
Femoral artery	150/50 (mean 75)	17.0 (91%)
Brachial artery	150/70	
Ascending aorta	140/80	
Left ventricle	140/4/20	

Blood O_2 capacity: 18.5 vol. %.
O_2 Consumption: 260 ml./min.

Systemic flow: $\frac{260}{17.0 - 10.0} = 3.7$ L./min.

Pulmonary flow: $\frac{260}{17.0 - 15.0} = 13.0$ L./min.

Left-to-right shunt: 9.3 L./min.

Table 1 summarizes the hemodynamic data obtained at right heart catheterization and during subsequent retrograde arterial studies. The abrupt increase in blood oxygen content in the right ventricle indicates a left-to-right shunt at the level of the outflow tract of the right ventricle. The slight degree of desaturation of arterial and "pulmonary capillary" blood is consistent with congestive heart failure. There is no evidence of a right-to-left shunt. The calculated flows and shunt are, of course, merely approximations, but do reveal a considerable left-to-right shunt with significantly reduced systemic flow.

In figure 3 are demonstrated the various pressure tracings obtained during right heart catheterization. Although the "pulmonary capillary" pressure is only moderately elevated

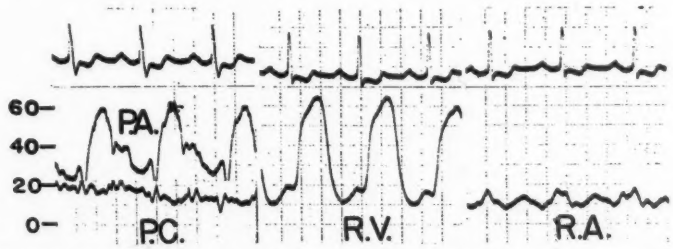


Fig. 3. Pressure curves obtained at right heart catheterization. Pressures in mm. Hg. Pulmonary artery (*P.A.*) and "pulmonary capillary" (*P.C.*) curves are superimposed, demonstrating considerable pulmonary artery hypertension with only a moderately elevated "capillary" pressure. The right ventricular (*R.V.*) diastolic pressure and right atrial (*R.A.*) pressure are high, indicating right ventricular failure. The normal pressure gradient across the tricuspid valve indicates normal function of that valve.

there is considerable pulmonary hypertension, indicating an increase in pulmonary arteriolar resistance. The right ventricular curve shows an elevated end-diastolic pressure preceded by a shallow diastolic "dip." The elevated right atrial pressure is consistent with the ventricular diastolic pressure, with the tricuspid valve functioning normally.

Following cardiac catheterization, a specially constructed balloon-tipped catheter was inserted via the same vein into the right atrium.[10] Approximately 40 ml. of 70 per cent Diodrast were instantaneously liberated in this chamber, while x-ray exposures at ½-second intervals were made. However, satisfactory visualization of the defect could not be obtained despite the large bolus of contrast material.

Retrograde aortic catheterization was carried out by means of a no. 7 cardiac catheter inserted via the left ulnar artery. Under fluoroscopic and manometric control, the catheter was advanced to the root of the aorta, and then through the aortic valve into the left ventricle. Repeated attempts were made to enter the suspected fistula, without success. However, during exploration of the left ventricle, the right ventricle was entered. The pressure transition from right ventricle to left ventricle to aorta established the presence of a ventricular septal defect (fig. 4).

In figure 5 are shown pressure curves from the left ventricle, ascending aorta, and the brachial and femoral arteries. The left ventricular curve exhibits a small diastolic dip and an anacrotic notch. The elevated end-diastolic pressure and "dip" are evidence of failure, with a relatively hypodynamic left ventricle. The aortic curve demonstrates a good incisura with a well maintained diastolic pressure. Even the brachial artery pulse pressure is somewhat less than would be expected from the cuff measurements. The femoral artery curve exhibits a significantly elevated pulse pressure.

Retrograde aortography was performed with the injection of 70 per cent Diodrast via the no. 7 catheter at the root of the aorta. However, it was impossible to obtain visualization of the ascending aorta by this method. The marked cardiac enlargement made x-ray penetration particularly unsatisfactory.

Subsequently, a thin-walled no. 8 catheter was inserted via the left brachial artery to the root of the aorta. During bilateral carotid artery compression, 20 ml. of 70 per cent Diodrast were rapidly injected 3 times, again with complete lack of visualization. Up to this point the patient had received a total of at least 110 ml. of 70 per cent Diodrast within a 6-month period, without untoward reaction.

Angiographic Demonstration of Fistula

Although immediate open-heart surgery was recommended in view of the probable diagnosis of cardioaortic fistula, there was considerable resistance to such an undertaking. It was argued that such possibilities as atypical patent ductus and aortic septal defect had not been adequately ruled out. As a matter of fact, in a patient ultimately proved to have a congenital aneurysm of a coronary artery[11] we had heard a murmur very similar to that in the present case.

Exploratory thoracotomy was strongly considered. In order to obviate such a move, a new diagnostic technic was developed and successfully employed:

Since rapid manual injection of 70 per cent Diodrast is particularly difficult via a long catheter (and against aortic pressure), an automatic injection apparatus was constructed. This consisted of a metal syringe, the tip of which was connected to the compressed air line via a simple stop-cock. The plunger of the syringe was fitted with a metal cap shaped to adapt to the barrel of a standard 50 ml. glass syringe. The 2 syringes were firmly mounted in series on a wood block, so that as compressed air forced the plunger back up the metal syringe, the barrel of the

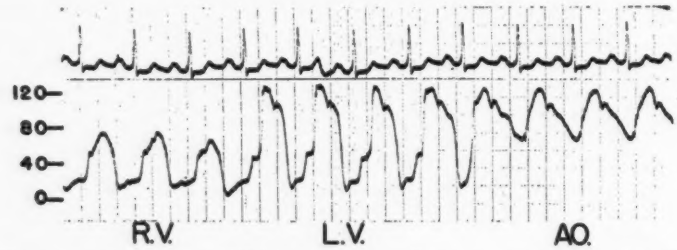


Fig. 4. Pressure curves during withdrawal of the catheter from right ventricle (*R.V.*) to left ventricle (*L.V.*) to aorta (*AO.*), demonstrating the presence of a ventricular septal defect.

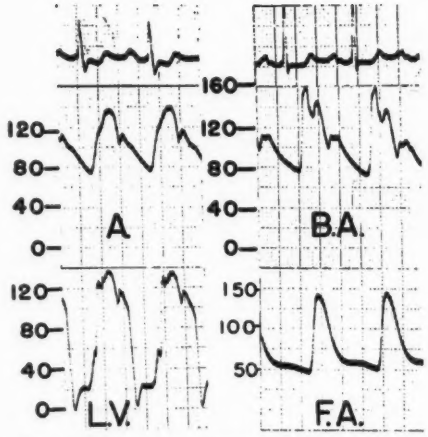


FIG. 5. Pressure curves from left ventricle (*L.V.*), ascending aorta (*A*), brachial artery (*B.A.*), and femoral artery (*F.A.*).

glass syringe was forced in, resulting in rapid ejection of the contained contrast material, with no danger of air embolism. With such an apparatus, 25 ml. of 70 per cent Diodrast could be injected via a no. 9 catheter in 1½ seconds.

However, even with rapid injection of large volumes of contrast material, we still failed to demonstrate the defect. It was then suggested that temporary reduction of ventricular ejection might encourage retrograde perfusion of the lesion with an adequate concentration of contrast material. Experimentally, it has been demonstrated that circulation can be reduced by means of increased intrathoracic pressure.[12]

In our extensive studies with unilateral pulmonary artery occlusion[9] and with intracardiac angiography[10] in unanesthetized patients, temporary circulatory occlusion had been produced inadvertently on a number of occasions. On 1 occasion in a patient with emphysema, the balloon-tipped catheter had been positioned in the right pulmonary artery. During inflation with 20 ml. of contrast material, the balloon had slipped into the main pulmonary artery producing complete occlusion for at least 15 seconds before it could be deflated. Although the patient complained of discomfort and shortness of breath, there were no alarming symptoms, and, within 1 minute of deflation, no residual effects.

In another patient suspected of having a patent ductus arteriosus, right pulmonary artery occlusion was carried out as part of a hemodynamic study. In this instance, unilateral occlusion produced a marked rise in main pulmonary artery pressure, with paroxysmal coughing and respiratory distress. The balloon was then deflated after about 20 seconds of occlusion of the right pulmonary artery and the patient was immediately comfortable, with no sequelae. Subsequent angiocardiographic studies revealed that this patient actually had congenital absence of the *left* pulmonary artery, so that temporary occlusion of his right pulmonary artery actually produced more or less total obstruction of pulmonary flow for a short period.

In a third patient, suspected of having an atypical patent ductus arteriosus, it was planned to inflate the Diodrast-filled balloon in the right pulmonary artery for an intracardiac angiogram. Accordingly, the tip of the special catheter was positioned in the right pulmonary artery. Fifty milliliters of 70 per cent Diodrast were then rapidly injected into the balloon and serial x-ray exposures were made as the contrast material was released. During this period the unanesthetized patient exhibited no particular distress. However, examination of the serial x-rays subsequently showed that the balloon had slipped back into the main pulmonary artery during inflation, so that the main pulmonary artery had been occluded for at least 10 seconds, without ill-effects.

These 3 experiences (and other lesser ones) suggested to the authors that temporary obstruction of circulation, even in the unanesthetized patient, was feasible, and could be performed if indicated. Accordingly, it was decided that circumstances justified its application in this patient. Of course, occlusion had to be planned so that the dynamic consequences would aid in demonstrating the suspected lesion; that is, if a left-to-right shunt were present, the contrast material would be encouraged to go from the site of injection at the root of the aorta into a lower pressure area. Technically, the easiest area for temporary occlusion is the main pulmonary artery. This would be indicated in a suspected patent

ductus, since distal pulmonary artery pressure would fall, facilitating shunting of contrast material from aorta to pulmonary artery. However, such a maneuver would tend to raise right ventricular pressure, so that if an aorta-right ventricular shunt were present, visualization would be impeded.

It appeared that the most likely site for obstruction would be at the inflow tract of the right atrium. A balloon catheter was constructed for simultaneous occlusion of both venae cavae. However, it was decided subsequently that inferior vena cava occlusion would suffice since, during retrograde aortic injection, circulation of the head and neck was manually occluded. Application of tourniquets to both arms could then provide almost complete obstruction of venous return to the heart.

One hour prior to the procedure the patient received secobarbital, 0.1 Gm. and meperidene hydrochloride, 50 mg. intramuscularly, which resulted in only mild sedation. A no. 9 thin-walled arterial catheter was inserted via the right brachial artery and advanced to the root of the aorta. During manipulation at this point a spot x-ray was taken, which subsequently was interpreted as showing the catheter tip traversing the fistula from the aorta into the right ventricle (fig. 6). (Comparison of this spot film with the final retrograde angiogram (fig. 7*B*) shows the catheter in the same approximate position as the fistula.) The catheter tip was then positioned just above the aortic valve (fig. 7*A*).

A balloon-tipped catheter was then inserted via the right brachial vein and advanced just into the

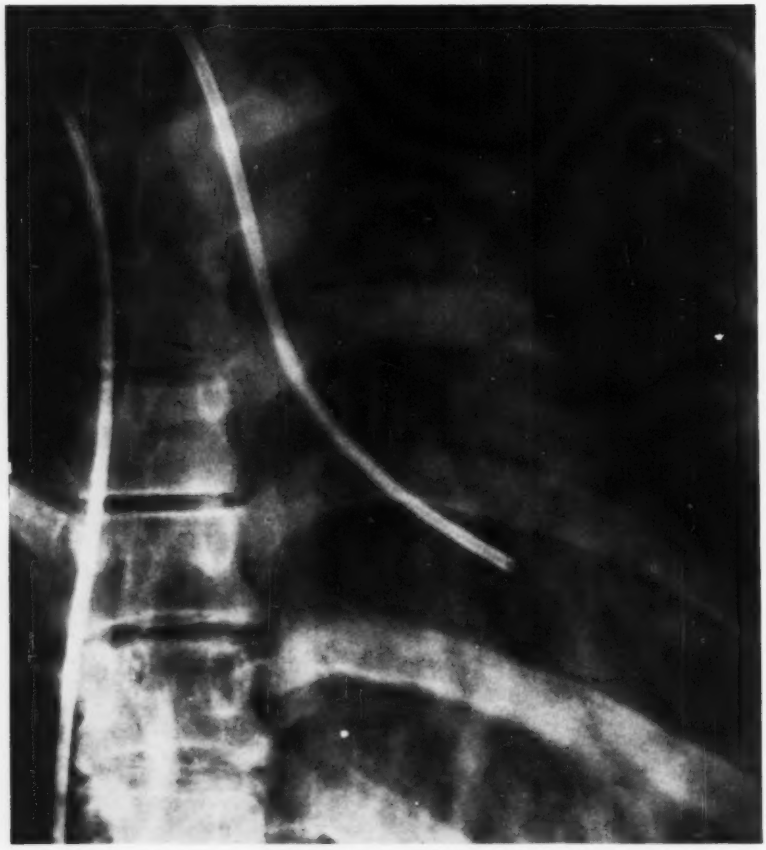


FIG. 6. Spot x-ray film during retrograde aortic catheterization showing aortic catheter traversing fistula from right sinus of Valsalva into right ventricle.

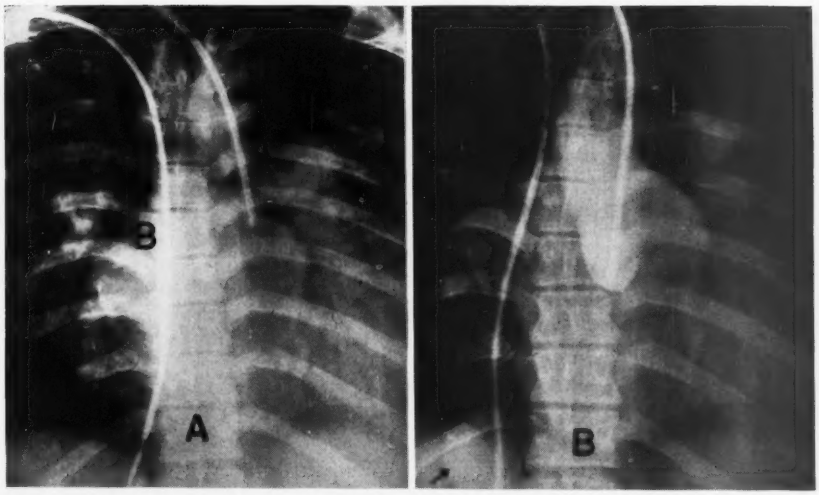


FIG. 7. *Left.* X-ray scout film showing retrograde aortic catheter tip (*A*) at base of the aorta. The balloon-tipped catheter (*B*) has been advanced through the right atrium so that its tip is in the inferior vena cava. *Right.* X-ray taken after retrograde injection of 25 ml. of 70 per cent Diodrast. The balloon occluding the inferior vena cava, containing 30 ml. of approximately 5 per cent Diodrast is faintly shown (small arrows). The aortic valve is competent. The large arrow points to the superior margin of the fistula extending from the right sinus of Valsalva into the right ventricle.

inferior vena cava (fig. 7*A*). Heparin, 50 mg., was given intravenously to prevent fibrin deposition on the catheters. The patient was then transferred via cart to the x-ray department, where he was placed in the anteroposterior position on the x-ray table. Suitable scout films were obtained.

In accordance with a well-rehearsed plan, the inferior vena cava was occluded by inflation of the balloon with 30 ml. of 5 per cent Diodrast, bilateral manual compression of the neck was applied, and 25 ml. of 70 per cent Diodrast were rapidly injected via the aortic catheter. A single x-ray exposure was made just at the end of injection. Immediately after exposure the inferior vena cava balloon was deflated; neck compression was released a few seconds later. More or less complete circulatory occlusion had been maintained for approximately 15 seconds. The patient exhibited remarkably little discomfort during the entire procedure. As a matter of fact, examination of the film revealed that the catheter tip had been displaced into the descending aorta so that excellent visualization of the arch and descending aorta was obtained, but not of the base. Accordingly, the catheter tip was repositioned and the entire procedure repeated. Again, there was little patient reaction despite another intra-aortic dose of 25 ml. of 70 per cent Diodrast. A few minutes later the patient was able to walk unsupported back to his bed. There were no further symptoms following the slight distress during the procedure. (The unintentional angiogram of the descending aorta revealed no evidence of a patent ductus arteriosus.)

Thus, after months of careful consideration and repeated failures, our efforts were finally crowned with success in the form of a single x-ray exposure (fig. 7*B*). Excellent visualization of the base of the aorta was obtained; a competent aortic valve is demonstrated. The small fistula is well shown (arrow). By virtue of its position, it was presumed to originate from the right sinus of Valsalva and to enter the right ventricle. The right ventricular chamber is not demonstrated. This x-ray was considered by all concerned as final proof of presence of a cardioaortic fistula, and there was then unanimous approval of the decision to proceed with open-heart surgery.

OPERATION

Operation was performed on August 28, 1956, by Dr. Melvyn Reydman. An artificial heart-lung machine with a bubble-type oxygenator was used. This machine is capable of maintaining a flow of at least 4 L. per minute. Induction of anesthesia was uneventful. An arterial catheter was inserted via the left femoral artery for continuous blood pressure

registration via a strain gage-oscilloscopic assembly. A trans-sternal incision provided adequate exposure. The heart was tremendously enlarged and dilated, so that manipulation was particularly difficult. As the various cannulations were being carried out in preparation for heart-lung by-pass, atrial tachycardia developed with a rate of 150 per minute. Within a few minutes ventricular fibrillation supervened. Manual cardiac massage was instituted, maintaining a satisfactory aortic pressure while final connections were made to the heart-lung apparatus. When the heart-lung machine had taken over, 25 ml. of approximately 5 per cent potassium citrate in blood were injected proximal to a clamp across the ascending aorta, thus perfusing the coronary bed and producing complete standstill of the fibrillating heart. A mean aortic pressure of 75 mm. Hg was maintained by the machine throughout.

The pulmonary artery was huge, as were the right ventricle and right atrium. Through a long right ventriculotomy incision excellent exposure of the outflow tract of the right ventricle was obtained. Just below the pulmonic valve, at the septum, could be seen the opening of the fistula, with a small crescent-shaped septal defect just below. An irregular gray-white area of thickened endocardium extended along the interventricular septum below the perforation. With the aid of a teflon plug, the combined ventricular openings were sutured closed. Perfusion of blood into the base of the aorta caused only a slight leakage into the right ventricle. As the ventriculotomy was closed gradual release of the aortic clamp allowed the heart to be perfused with blood. The potassium was flushed from the coronary arteries. At this point the huge heart almost filled the thoracic cavity. Despite vigorous and prolonged cardiac massage and other resuscitative procedures, the heart beat could not be restored. An autopsy was performed.

Postmortem Examination of the Heart (Figs. 8*A* and *B*)

The heart weighed 820 Gm. The aorta was normal in size. The aortic valves were not deformed and there was no aortic incompetence. The coronary arteries were normal. The pulmonary artery, right ventricle, and right atrium were markedly enlarged. The right ventricle measured 1.1 cm. in thickness. At the base of the right sinus of Valsalva was an aneurysm that protruded into the outflow tract of the right ventricle. At the tip of this aneurysm was a round perforation 4 mm. in diameter. Adjacent to the perforation there was a somewhat larger crescent-shaped ventricular septal defect. An irregular endocardial "jet lesion" extended below the perforation. Grossly and microscopically the combined defects were quite similar to those described by Edwards and co-workers[13, 14] and Lin and co-workers.[15] As a matter of fact, the physiologic findings were also remarkably similar in most respects.

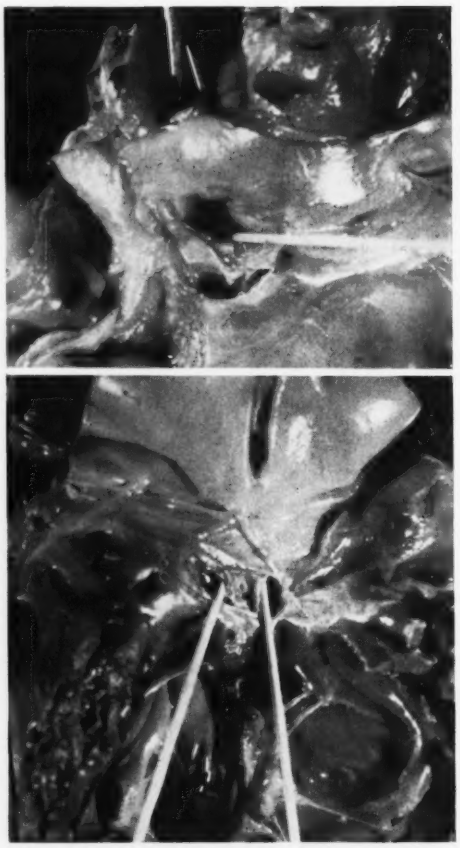


Fig. 8. Autopsy specimen. (All sutures have been removed.) *Top.* View of aortic valve region. (Right coronary cusp deflected downward.) Probe is in aneurysm of right sinus of Valsalva. Perforation can be seen at base. (Other perforation is artifact.) Crescent-shaped interventricular septal defect just below cusp. *Bottom.* Right ventricular view. Probe on right is in septal defect. Probe on left is in perforation. Arrow points to "jet lesion."

Discussion

At this time, fewer than 50 cases of rupture of a sinus of Valsalva have been reported. Within the past year, however, isolated cases

have appeared with increased frequency. On occasion, only after exploratory operation has the correct diagnosis been established.[15] Following a definitive diagnosis, operation has been carried out in 3 reported cases,[2, 3, 16] all as open-heart procedures. In 2 patients an artificial heart-lung was used,[2, 16] and in the other, hypothermia.[3] Unfortunately, in both patients operated with the artificial heart-lung, the outcome was the same as in our case. The operation under hypothermia was successful, but the patient died 14 days postoperatively of overwhelming infection. At this writing, there have been no reported cases of long-term survival after operation.

Technically, the lesion is amenable to surgery. However, operation must be performed as soon as possible after rupture has occurred. The duration of life after rupture has been reported as 7 days to 7 years.[2] As in the case herein reported, a remarkable degree of hypertrophy and dilatation may occur in a short time, even though the fistula is relatively small. Presumably, a stage of irreversible failure is soon reached, so that even with successful closure of the defect, there may be no reversal of the deteriorating course.

This case demonstrates the remarkable difference in hemodynamic consequences of congenital shunts as compared to those that are suddenly acquired. Even large congenital shunts are usually well tolerated for many years, with lesser degrees of hypertrophy and dilatation. In this patient, the calculated shunt flow from left-to-right was approximately 9 L. per minute. By modifying the patent ductus formula of Gorlin and Gorlin,[17] it can be calculated that a fistula of the size produced by the perforation in this case would give a shunt flow of less than 3 L. per minute, with 6 L. per minute shunting through the ventricular defect. Thus, although the interventricular shunt presumably had been well tolerated, a sudden 50 per cent increase in the shunt produced dire consequences associated with marked hypertrophy and dilatation. Although some degree of cardiac enlargement may have preceded the rupture in this case, there was no clinical evidence to that effect.

The clinical and pathologic aspects of unruptured and ruptured aneurysms of the sinuses of Valsalva have been reviewed by others.[2, 3, 5, 6, 14, 15] Edwards and Burchell[14] have demonstrated that the basic lesion in such cases is always the same: A lack of continuity between the aortic media and the ring of the aortic valve. The right coronary sinus, from which the right coronary artery originates, is most frequently involved, and anatomic relationships are such that it most frequently ruptures into the right ventricle. In the case reported, the defect in the ventricular membranous septum is, presumably, merely an extension of this congenital lack of continuity.

The ruptured sinus of Valsalva appears to be much more common in males, with ages varying from 20 to 67 (average: 42 years). Although there is usually severe pain at the onset, our patient exhibited only sudden severe dyspnea but not pain.

The murmur associated with the fistula is usually very loud and continuous throughout the cardiac cycle. As in our case, rupture into the right ventricle produces a murmur of maximum intensity in the third left intercostal space that seems to radiate toward the apex. The pulmonic second sound is accentuated and is associated with increased pulmonary artery pressure and flow.

The collapsing pulse and wide pulse pressure indicate a rapid aortic run-off. It is interesting to note that the sphygmomanometric pulse pressure was much greater than the actual direct brachial artery determination. Furthermore, the lowest diastolic recording was in the femoral artery, whereas the pressure in the ascending aorta (near the site of the fistula) was essentially normal.

X-ray changes are not specific. Generally, there is marked cardiac enlargement, with increased pulmonary blood flow. The electrocardiogram usually shows the pattern of combined hypertrophy.

Cardiac catheterization has been carried out in a number of reported cases[1-4, 13, 15] with demonstration of a left-to-right shunt. Of course, right heart catheterization does not demonstrate the origin of the shunt. However, given evidence of an interventricular septal defect, with a wide pulse pressure, rupture of a

sinus of Valsalva into the right ventricle should be considered.

Although unruptured aneurysms have been demonstrated by angiocardiography,[7, 8] we know of only 2 cases presumed to have ruptured aneurysms in which there was angiocardiographic confirmation.[7] However, in only 1 of these was there retrograde demonstration of a defect, (neither with autopsy confirmation). We believe the case reported to be the first proved cardioaortic fistula demonstrated by retrograde visualization of the fistula.

The technic of temporary circulatory occlusion was particularly effective in this case in enabling us to visualize the defect. Although there is an obvious real risk in its use, it has been demonstrated that the technic can be applied effectively under special circumstances. As a matter of fact, variations of this technic are now being applied in this laboratory in a number of diagnostic problems.

Summary

Sudden rupture of an aneurysm of a sinus of Valsalva results in a dramatic clinical picture, with a rapidly progressive, deteriorating course. Most frequently, the right sinus of Valsalva ruptures into the right ventricle, as in the case presented. A loud continuous murmur and thrill, wide pulse pressure, and hemodynamic evidence of a left-to-right interventricular shunt characterize this cardioaortic fistula.

Definitive diagnosis was finally accomplished in this case only with the aid of a new technic: Temporary circulatory occlusion (inferior vena cava occlusion by a balloon and bilateral manual compression of the neck) adequately reduced circulation to enable visualization of the cardioaortic fistula by means of contrast material injected via an aortic catheter. The markedly hypertrophied heart failed during open-heart surgery; function could not be restored following repair. Early recognition and repair, before a stage of irreversibility is reached, is mandatory for a condition that is appearing with increased frequency.

Summario in Interlingua

Le ruptura subitanee de un aneurysma del sinus de Valsalva resulta in un frappante situation clinic con rapide e progressive deterioration. In le majoritate del casos, le sinus dextere de Valsalva es le sito del ruptura, con apertura verso le ventriculo dextere. Isto esseva le situation in le caso hic presentate. Iste typo de fistula cardioaortic es characterisate per un forte e continue murmure, un late pression pulsatil, e signos hemodynamic de un derivation interventricular sinistro-dextere.

In nostre caso le diagnose definitive esseva finalmente effectuate per medio de un nove technica. Un occlusion temporari del circulation esseva inducite per medio de un ballon in le vena cave inferior insimul con le compression manual de ambe lateres del cervice. Le resultante reduction circulatori sufficeva pro render possibile le visualisation del fistula cardioaortic per medio de un substantia de contrasto que esseva injicite via un catheter aortic. Le corde esseva marcatemente hypertrophiate. Illo disfalleva durante le operation a corde aperte, e su function non poteva esser restablite post que le reparo esseva completate. Precoce recognition del presentia de un fistula cardioaortic e prompte intervention chirurgic ante le advenimento del stato de irreversibilitate es indispensabile in le tractamento de iste condition que occurre con crescente frequentias.

REFERENCES

[1] Arias, C. A., and Baudino, C.: Aneurisma congenita de un seno de valsalva ruptura en cavidades derechas. Rev. argent. cardiol. **19:** 72, 1952.

[2] Oram, S., and East, T.: Rupture of aneurysm of aortic sinus (of Valsalva) into the right side of the heart. Brit. Heart J. **17:** 541, 1955.

[3] Brown, J. W., Heath, D., and Whitaker, W.: Cardioaortic fistula: A case diagnosed during life and treated surgically. Circulation **12:** 819, 1955.

[4] Kjellberg, S. R., Mannheimer, E., Rudhe, V., and Jonsson, B.: Diagnosis of Congenital Heart Disease. Chicago, The Year Book Publishers, Inc., 1955, p. 442.

[5] Venning, B. M.: Aneurysm of the sinuses of Valsalva. Am. Heart J. **42:** 57, 1951.

[6] Jones, A. M., and Langley, F. A.: Aortic sinus aneurysms. Brit. Heart J. **11:** 325, 1949.

[7] Steinberg, I., and Finby, N.: Clinical manifestations of the unperforated coronary sinus aneurysm. Circulation **14:** 115, 1956.

[8] Falholt, W., and Thomsen, G.: Congenital an-

eurysm of the right sinus of Valsalva. Diagnosed by aortography, Circulation **8:** 549, 1953.

[9] Brofman, B. L., Charms, B. L., Kohn, P. N., Elder, J. C., Newman, R., and Rizika, M.: Unilateral pulmonary artery occlusion in man. Control studies. J. Thoracic Surg. In press.

[10] —: Intracardiac angiography: Controlled instantaneous intra-atrial release of contrast material in man. J. Thoracic Surg. **32:** 28, 1956.

[11] Mozen, H. E.: Congenital cirsoid aneurysm of a coronary artery with associated arterio-atrial fistula, treated by operation. Ann. Surg. **144:** 215, 1956.

[12] Boerema, I., and Blickman, J. R.: Reduced intrathoracic circulation as an aid in angiocardiography. An experimental study. J. Thoracic Surg. **30:** 129, 1955.

[13] Edwards, J. E., Dry, T. J., Parker, R. P., Burchell, H. B., Wood, E. H., and Bulbulian, A. H.: An Atlas of Congenital Anomalies of the Heart and Great Vessels. Springfield, Ill., Charles C Thomas, 1954, p. 124.

[14] —, and Burchell, H. B.: Specimen exhibiting the essential lesion in aneurysm of the aortic sinus. Proc. Staff Meet., Mayo Clin. **31:** 407, 1956.

[15] Lin, T. K., Crockett, J. E., and Dimond, E. G.: Ruptured congenital aneurysm of the sinus of Valsalva. Am. Heart J. **51:** 445, 1956.

[16] Kirklin, J. W., *quoted by* Burchell, H. B.: Unusual forms of heart disease. Circulation **10:** 574, 1954.

[17] Gorlin, R., and Gorlin, S. G.: Hydraulic formula for calculation of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. Am. Heart J. **41:** 1, 1951.

Rosenthal, R. L.: Over-all Coagulability in Patients Receiving Dicumarol Therapy with Emphasis on Acute Myocardial Infarction. J. Lab. Clin. Med. **47:** 611 (April), 1956.

The author discusses the measurement of over-all coagulability during Dicumarol therapy as indicated by measurement of the clotting time at both room temperature and at 37 C., the 4-gamma and 1-gamma heparin clotting time (HCT) and the 1-stage prothrombin time (PT). Serial coagulation studies were performed on 21 patients receiving Dicumarol and an index of over-all coagulability was obtained from the ratio of the HCT to the PT. The PT showed a rough correlation with other clotting tests, particularly with the heparin clotting time. The author attributed this to the limitations of the PT, which measured only 1 phase of the clotting mechanism and did not reflect changes in the thromboplastic factors (platelets, antihemophilic globulin, plasma thromboplastin component, plasma thromboplastin antecedent, etc.). These factors may be affected by Dicumarol (particularly PTC), or the patient's disease. The studies on patients with acute myocardial infarction revealed hypercoagulability fluctuating with hypocoagulability, superimposed on the Dicumarol effects. Hemorrhagic manifestations seemed more closely related to over-all coagulability than to prothrombin time alone.

The significance of the over-all coagulability in the control of anticoagulant therapy with Dicumarol and related drugs, particularly in relation to acute myocardial infarction was discussed. These studies suggested that the prothrombin time may be inadequate as the basis of a therapeutic range and in control of therapy with Dicumarol and related compounds.

Maxwell

Electrocardiographic Abnormalities in Epidemic Hepatitis

By L. M. Sanghvi, M.R.C.P., (Lond.), D.T.M. & H. (Eng.), and S. N. Misra, M.B.B.S.

Myocarditis has been reported in patients dying with viral hepatitis. With the increasing incidence of the disease, recognition of myocardial involvement is apparently important. The nature of the abnormalities suggested several factors including ischemia and local electrolyte disturbance of myocardium. The incidence of abnormalities was greater in the out-patients and in those with tachycardia, and greatest at the peak of the epidemic. Abnormalities showed no relation to the severity of the jaundice or of the illness or to the serum protein levels.

MYOCARDITIS not infrequently occurs in virus diseases such as anterior poliomyelitis, mumps, measles, varicella, infectious hepatitis, and primary pneumonia.[1] The electrocardiogram may be the basis of diagnosing myocardial involvement in viral diseases because other manifestations are often absent or minor. Myocardial changes in epidemic viral hepatitis have been infrequently reported in the literature[2-6] and there are few comprehensive studies of electrocardiographic changes with multiple lead records. The incidence of viral hepatitis appears to be on the increase and recognition of myocardial involvement may prevent cardiac catastrophies or residual changes by allowing sufficient convalescence. Therefore, when an epidemic of viral hepatitis occurred in Jaipur in 1955, the present investigation was undertaken to determine the incidence and the nature of the electrocardiographic abnormalities and their relation to various clinical and other factors.

Material and Methods

One hundred forty patients with jaundice due to epidemic hepatitis but without other cardiovascular disease were studied. Fifty-seven patients, of whom 10 were comatose, were admitted to the hospital; 83 attended the out-patient department. There were 127 males and 13 females with ages varying from 8 to 55 years. The duration of illness at the time of first observation varied from 1 day to 22 weeks. Electrocardiograms with standard leads, I, II, III, and unipolar leads, aV_R, aV_L, aV_F, and V_1 to V_6 were recorded routinely and additional chest leads were taken in a few cases. Serial tracings were recorded in all in-patients and a large majority of the out-patients. In patients with hepatic coma tracings were often repeated twice a day. Sinus tachycardia or bradycardia by itself and minor changes in the amplitude of the QRS were not considered abnormal. Changes of P and T waves were considered as abnormalities only if they became normal on serial observations. A Q-T ratio of more than 1.09 in males and 1.08 in females[7] was considered abnormally prolonged. Icterus index, total serum proteins, and serum albumin and globulin were determined and repeated, particularly when the electrocardiogram showed any abnormality.

From the Department of Cardiology, Sawai Man Singh Hospital and Medical College, Jaipur, India.

Results

Electrocardiographic Findings

Definite abnormalities were confirmed by serial tracings in 61 cases and are summarized in table 1.

Rate and Rhythm. The cardiac rate was 90 or more in 23 cases, 60 or less in 28 cases, and 61 to 89 in 89 cases. The incidence of abnormal electrocardiograms in cases with tachycardia was nearly twice as high as in those with bradycardia (table 2). Premature ventricular beats were seen in 2 cases and nodal rhythm in 1 case.

P Wave. Abnormal P waves were seen in 10 cases: they consisted of broad or tall P waves, more than 0.12 mm. wide or 3 mm. high in 6 cases, and inverted P in 4 cases. The abnormality was never isolated but always associated with some other abnormality in the electrocardiogram.

QRS Complex. Slight increase or diminution in the amplitude of QRS after recovery occurred with nearly equal frequency. A pattern of left ventricular hypertrophy was seen in 1

TABLE 1.—*Summary of Electrocardiographic Abnormalities in Sixty-one Cases*

Abnormalities	No. of cases
P changes	10
T changes	48
S-T segment depressed	24
Q-T interval prolonged	6
Conduction defects	3
Ventricular premature beats	2
Left ventricular hypertrophy	1
Hypopotassemia	2

TABLE 2.—*Incidence of Cases with Abnormal Electrocardiograms According to Cardiac Rate*

Cardiac rate	Total cases	No. with abnormalities
60 or less	28	9 (32%)
90 or more	23	15 (65%)
61–89	89	37 (41%)
Total	140	61

case, and QRS duration of 0.13 second, suggesting intraventricular conduction defect, occurred in another.

S-T Segment and T Wave. Changes in the S-T segment and T wave were the most frequent abnormalities. S-T depression was seen in 24 cases and occurred most frequently in leads II, III, aV_F and V_{4-6}. Changes in T wave were seen in 48 cases and included tall T in 4 cases, low voltage or flat T in 29 cases, abnormal contour with broad or bifid summit in 7 cases, and inverted T in 35 cases. They occurred most frequently in leads III, aV_L, aV_F, and V_{1-3}. In 2 cases T waves were inverted in all the precordial leads.

T inversions were of different patterns: (1) "Coronary T-wave pattern"[8] with pointed apex or terminal dipping of T in 9 cases; (2) inversion of initial segment with S-T depression but upright terminal T in 17 cases; (3) complete inversion of T with S-T depression of the "straight line type" in 7 cases; and (4) hammock-like depression of S-T segment with inverted T and elevated U wave suggesting a hypopotassemia pattern in 2 cases.

An interesting finding was isolated T-wave negativity in precordial leads in the topographic sense in that the flanking leads showed these changes to a much lesser extent or showed upright T waves. This was seen in 5 cases, in 3 cases in V_3 only and in 1 case each in V_{3-4} and V_{2-4} (fig. 1). These changes were transient, the T wave becoming upright within 3 to 11 days. All the 5 patients were between 20 to 27 years of age and 3 of them were females, the possibility of coincident coronary artery disease being therefore very little. Q-T ratio increased in 2 and decreased in 3 of them by more than 0.06 when the electrocardiogram returned to normal, but it was not prolonged above normal limits in any of them. An exercise test, done after recovery in 2 cases, was negative.

U Wave. There was isolated inversion of U in lead V_3 in 1 case (fig. 1).

Conduction Defects. These were seen in 3 cases. In 1 case the duration of QRS was 0.13 second, suggesting intraventricular defect. In another case the P-R interval was prolonged to 0.22 second, returning to normal later. The third case showed at various stages of the illness complete heart block, second degree heart block, and prolonged P-R interval of 0.38 second (fig. 2). Prolongation of P-R in this case has persisted up to the present nearly a year after recovery from the illness. During the illness in the hospital this patient had suddenly developed tachycardia, gallop rhythm, and a systolic murmur indicating onset of acute myocarditis.

Q-T Interval. The Q-T ratio was increased in 6 cases ranging from 1.14 to 1.35. Three of these cases were in hepatic coma of whom 2 died. The 2 fatal cases showed a pattern of hypopotassemia. One had jaundice for 16 weeks and was comatose for 48 hours prior to admission, and died within a few hours of the recording of the electrocardiogram, so that estimation of serum potassium could not be done. The second case had had jaundice for 20 weeks before admission when the first electrocardiogram recorded showed these changes (fig. 3). She became comatose 48 hours later and died on the eighth hospital day. Repeated estimation of serum potassium revealed normal values and administration of potassium chloride produced no significant alteration in the electrocardiogram.

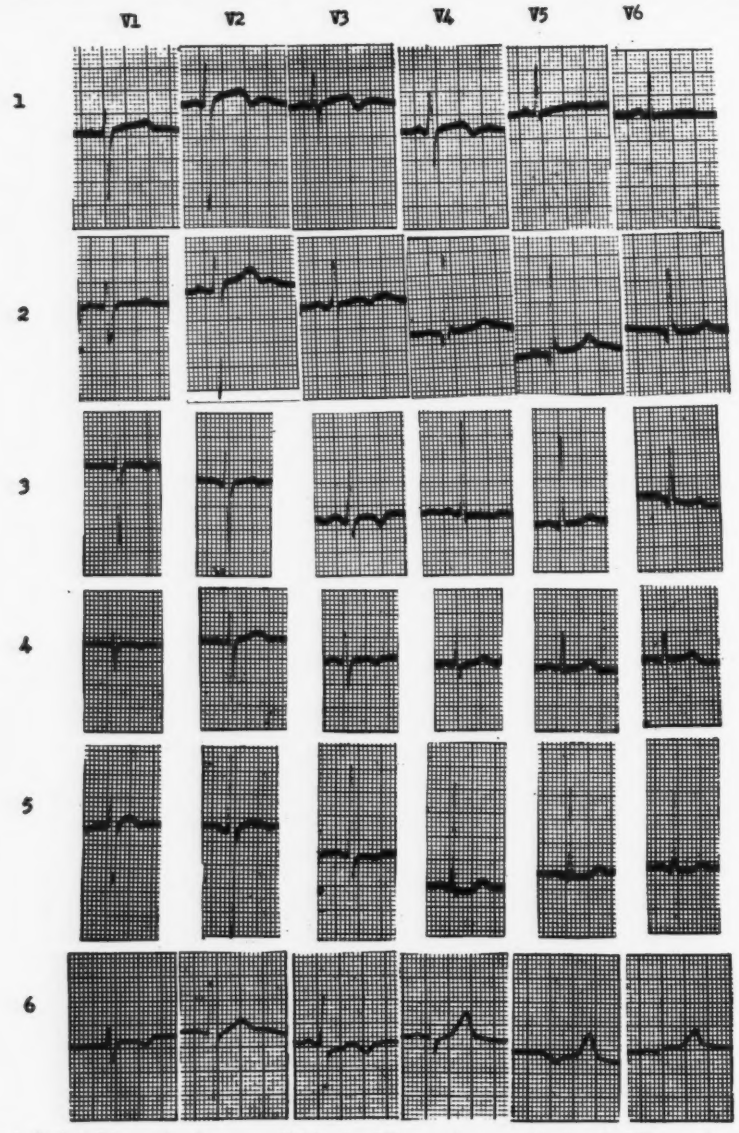


FIG. 1. Isolated inversion in precordial leads of T wave in cases 1 to 5 and of U wave in case 6

Correlation of Electrocardiographic Abnormalities with Other Factors

Electrocardiograms were abnormal in 40 (48 per cent) of the 83 out-patients and 21 (37 per cent) of the 57 in-patients, the incidence of abnormalities being greater in the former even though the tracings were repeated less often and the severity of the illness was comparatively less in them than in the in-patients. It is likely that the greater activity of the out-patients who were often ambulatory may have produced a greater stress on the myocardium.

The incidence of cases with abnormalities according to the date of onset of illness was

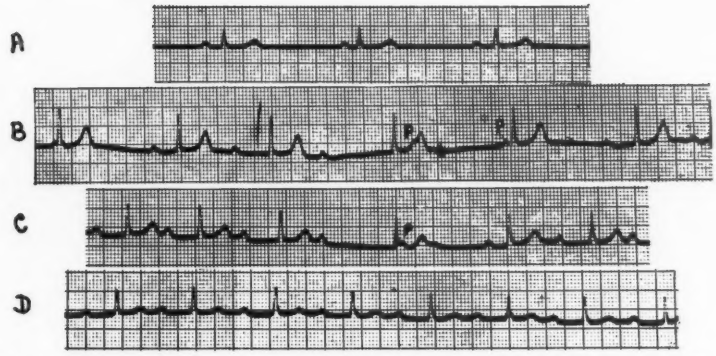


FIG. 2. Various grades of heart block at different times in the same patient. *A*. Normal sinus rhythm with bradycardia. *B*. Complete heart block. *C*. Partial heart block with Wenckebach phenomenon. *D*. Prolonged P-R interval of 0.38 second.

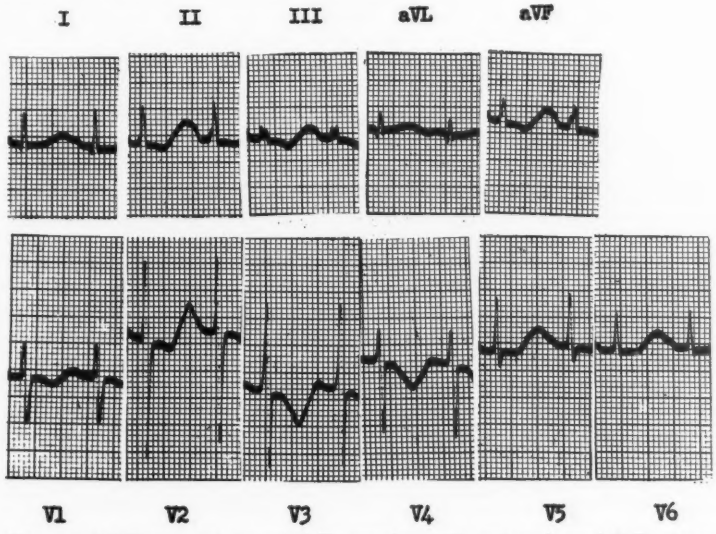


FIG. 3. Depressed S-T segment, inverted T, prominent U, and prolonged Q-T, changes characteristic of hypopotassemia in a female patient who died later.

TABLE 3.—*Incidence of Cases with Abnormal Electrocardiograms According to the Month of Onset of Disease*

Month	Total cases	No. with abnormalities
Aug. 1955	3	1 (33%)
Sept. 1955	16	5 (31%)
Oct. 1955	19	5 (26%)
Nov. 1955	23	14 (61%)
Dec. 1955	30	20 (66%)
Jan. 1956	27	11 (40%)
Feb. 1956	11	2 (18%)
March and April 1956	11	3 (27%)
Total	140	61

greatest at the height of the epidemic (table 3) and suggested some relationship to the epidemiology of the infection.

Incidence of abnormalities was not related to the severity of the jaundice as determined by the icterus index (table 4) nor was it related to the severity of the illness. For example, 4 of the 10 patients with hepatic coma had normal tracings. Myocardial involvement as suggested by abnormal electrodardiograms in the other 6 cases did not indicate a grave prognosis either, as 4 of them recovered.

Abnormal and normal electrocardiograms

TABLE 4.—*Incidence of Cases with Abnormal Electrocardiogram According to Icterus Index*

Icterus index	Percentage of cases with abnormalities
0–25	40
26–50	60
51–100	46
above 100	50

were seen with equal frequency in cases with normal serum protein values as well as in those with diminished proteins and reversal of albumin-globulin ratio. Abnormalities appeared at any time from the first day to the twentieth week of the illness and were usually transitory in nature. In only 1 instance did the abnormality, a prolonged P-R interval, persist.

DISCUSSION

Isolation of the "encephalomyocarditis" virus[9, 10] from the myocardium of anthropoid apes who apparently died of myocarditis and of the poliomyelitis virus[11] from the hearts of patients dying of this disease suggests the possibility that the virus may directly attack the myocardium in certain viral diseases. The derangement of myocardial function evidenced by electrocardiographic changes may, however, be due to elements other than specific myocarditis including extracardiac variables in the form of chemical, pharmacologic, thermal, and metabolic influences; alterations in the tone of extrinsic cardiac nerves; and the cardiac causes like pre-existing valvular disease or myocardial necrosis.

In epidemic hepatitis myocardial changes have been reported in the literature in the form of diffuse serous inflammation, foci of necrosis of isolated muscle fibers, changes in the bundle of His[6], hemorrhages in the heart[2], interstitial and perivascular cellular infiltration, parenchymal degeneration described as myocardosis,[12] and hemorrhagic pericardial exudate.[5] The electrocardiographic changes in hepatitis have been attributed to concentration of bile in the blood, changes in serum proteins, electrolyte disturbances, autonomic imbalance, myocardial anoxia, and specific virus myocarditis.[13]

In the present investigation cardiac causes and pharmacologic and thermal influences were excluded. The abnormalities appeared to have some relation to the epidemiology of the infection, the activity of the patient, and the cardiac rate, but no relation to the severity of the jaundice, the severity of the illness, and the serum protein levels. The isolated negativity of T or U-wave seen in this series does not appear to have been reported previously in hepatitis. T negativity, limited to or about the lead V_4, has been reported in healthy males.[14] In all our cases the T waves became upright later. Schlant and co-workers[15] suggested that isolated T negativity represented the clinical counterpart of an ischemic phase of myocardial infarction. It may occur in stress tests indicating a positive test of coronary insufficiency. Inversion of U wave has been found in coronary artery disease.[16] These changes therefore suggested that ischemia of the myocardium was one of the factors responsible for electrocardiographic abnormalities.

Prolongation of the Q-T interval in viral hepatitis has been interpreted as insufficiency of cardiac energy[17] and disturbance of cardiac metabolism with diffuse myocardial involvement.[13] Of the 6 cases with this abnormality in this series 3 were in hepatic coma. Two of these comatose patients also showed other severe abnormalities, suggesting the pattern of hypopotassemia, and died. Four patients, however, recovered without any residual changes. According to Lyon[13] the prolonged Q-T is not found in the early icteric stage of the disease but takes some time to develop and is then found in less severe cases. In the present series it was seen as early as the fourth day of the illness and with an icterus index as high as 150.

Occurrence of various grades of heart block during the illness in 1 case was suggestive of lesions in the bundle of His described by Saphir and co-workers;[6] persistence of the prolonged P-R interval in this case indicated permanent isolated damage in the bundle. That the electrolyte disturbance may be local in the myocardium and not be present in the blood was indicated by the normal values of serum potassium in 1 of the 2 cases with changes characteristic of hypopotassemia in which these determinations were made.

Recently, Saphir and co-workers[6] found

acute myocarditis in 4 of the 6 patients dying with viral hepatitis and recommended electrocardiographic studies in every patient with hepatitis. The present study showed a high incidence of abnormalities and their nature suggested that myocardial ischemia, diffuse disturbance of myocardial metabolism, lesions of the bundle of His, and local electrolyte disturbance in the myocardium, were some of the factors contributing to the abnormalities.

It is, however, difficult to evaluate the significance of the myocardial involvement demonstrated by these abnormalities. In spite of their high incidence there was only a single instance of a residual abnormality, in the form of prolonged P-R interval. This patient was an in-patient who had proper bed rest and treatment at the time of the acute myocarditis, and the heart block persisted despite a prolonged convalescence. Again 6 of the 10 patients in hepatic coma showed abnormalities but only 2 died; they showed the most severe changes of a hypopotassemic pattern and had a prolonged illness of more than 4 months. These 2 were the only fatal cases in the entire series. To what extent the myocardial involvement contributed to the death of these 2 patients is difficult to estimate, especially because unfortunately necropsy could not be obtained. It seems possible, however, that at least in 1 of them in whom the serum potassium was determined and was normal, the death was due to local electrolyte disturbance and severe myocardial damage.

Summary

One hundred forty patients with jaundice due to epidemic hepatitis were studied to determine the incidence and the nature of the electrocardiographic abnormalities and their relation to several factors.

Abnormalities were found in 61 (44 per cent) cases and included T changes in 48 cases, S-T depression in 24 cases, conduction defects in 3 cases, prolonged Q-T in 6 cases, and a hypopotassemic pattern in 2 cases. An interesting feature was isolated negativity of the T wave in 5 cases and of the U wave in 1 case in the precordial leads.

The incidence of abnormalities was greater in the out-patient and in those with tachycardia, and greatest at the peak of the epidemic, suggesting some relation to the activity of the patient, the cardiac rate, and the epidemiology of the infection. These abnormalities were not related to the severity of the jaundice, the severity of the illness, or the serum protein levels.

The nature of the abnormalities suggested that myocardial ischemia, diffuse myocardial derangement, lesions of the bundle of His, and local electrolyte disturbance in the myocardium were some of the contributing factors.

Cardiac damage persisted in only 1 patient.

Summario in Interlingua

Esseva studiate 140 patientes con jalnessa resultante de hepatitis epidemic pro determinar le incidentia e le natura de anormalitates electrocardiographic e lor relation a varie factores.

Anormalitates esseva trovate in 61 casos (44 pro cento). Illos includeva alterationes de T in 48 casos, depression de S-T in 24, defectos de conduction in 3, prolongation de Q-T in 6, e un configuration hypokalemic in 2. Un aspecto interessante esseva isolate negativitate del unda T in 5 casos e del unda U in 1 caso in le derivationes precordial.

Le incidentia de anormalitates esseva plus alte inter patientes visitante e inter patientes con tachycardia e maximal al culmine del epidemia. Isto pareva indicar un influentia exercite per le activitate del patiente, le velocitate cardiac, e le epidemiologia del infection. Iste anormalitates non esseva relationate al severitate del jalnessa, al severitate del morbo, o al nivellos seral de proteina.

Le natura del anormalitates suggereva que le factores responsabile includeva ischemia myocardial, diffuse disrangiamento myocardial, lesiones del fasce de His, e local disturbationes electrolytic in le myocardio.

Le insulto cardiac persisteva in solmente 1 patiente.

REFERENCES

[1] Saphir, O.: Virus myocarditis. Mod. Concepts Cardiovas. Dis. **6:** 43, 1949.

[2] Lucke, B.: Pathology of fatal epidemic hepatitis. Am. J. Path. **20:** 471, 1944.

[3] Wood, D. A.: Pathological aspects of acute epidemic hepatitis with special reference to early stages. Arch. Path. **41:** 345, 1946.

[4] Lyon, E.: Myocarditis in virus diseases of man. Med. Rec. **160:** 403, 1947.

[5] Eisen, J. M., and Markovich, V.: Fatal acute hepatitis: Report of a case with massive hemorrhage in pericardial and pleural cavities. J. A. M. A. **146:** 1414, 1951.

[6] Saphir, O., Amronin, G. D., and Yokoo, H.: Myocarditis in viral hepatitis. Am. J. M. Sc. **231:** 168, 1956.

[7] Goldberger, E.: Unipolar Lead Electrocardiography and Vectorcardiography. Philadelphia, Lea and Febiger, 1953.

[8] Pardee, H. E. B.: Clinical Aspects of Electrocardiogram Including Cardiac Arrhythmias. London, H. K. Lewis & Co., 1941.

[9] Helwig, F. C., and Schmidt, E. C. H.: A filter passing agent producing interstitial myocarditis in anthropoid apes and small animals. Science **102:** 31, 1945.

[10] Schmidt, E. C. H.: Virus myocarditis: Pathologic and experimental studies. Am. J. Path. **24:** 97, 1948.

[11] Jungeblut, C. W., and Edwards, J. E.: Isolation of the poliomyelitis virus from the heart in fatal cases. Am. J. Clin. Path. **21:** 601, 1951.

[12] Lyon, E.: Myocardosis of infective hepatitis. Israel M. J. **10:** 139, 1951. Abstracted Circulation **5:** 309, 1952.

[13] —: Viral Diseases and the Cardiovascular System: A Survey. New York and London, Grune and Stratton, Inc., 1956.

[14] Grant, R. P., Estes, E. H., Jr., and Doyle, J. T.: Spatial vector electrocardiography: The clinical characteristics of S-T and T vectors. Circulation **3:** 182, 1951.

[15] Schlant, R. C., Levine, H. D., and Bailey, C. C.: "Isolated" T-wave negativity in the "ischemic phase" of myocardial infarction in man. Circulation **10:** 829, 1954.

[16] Nisnewitz, S., Stein, I., Silverstone, F., and Slatter, S. R.: The inverted U wave in coronary artery disease. New York State M. J. **54:** 2078, 1954.

[17] Hegglin, R.: Klinik der energetisch—dynamischen Herzinsuffizions, Cardiologia **15:** 65, 1949; Cited by Lyon.[13]

As to your method of work, I have a single bit of advice, which I give with the earnest conviction of its paramount influence in any success which may have attended my efforts in life—Take no thought for the morrow. Live neither in the past nor in the future, but let each day's work absorb your entire energies, and satisfy your widest ambition. That was a singular but very wise answer which Cromwell gave to Bellevire—"No one rises so high as he who knows not whither he is going," and there is much truth in it. The student who is worrying about his future, anxious over the examinations, doubting his fitness for the profession, is certain not to do so well as the man who cares for nothing but the matter in hand, and who knows not whither he is going.—William Osler, To His Students, 1849–1919.

The Normal Vectorcardiogram and a System for the Classification of Vectorcardiographic Abnormalities

By W. R. Milnor, M.D.

The essentially 3-dimensional nature of the spatial vectorcardiogram (sVCG) requires that it be studied as a vector sequence in space, and not merely in its projections on the arbitrary frontal, sagittal, and transverse planes. One striking characteristic of the normal QRS sÊ-loop is that it lies approximately in a single "plane of predilection," which does not coincide with any of these 3 arbitrary planes. This paper describes the variations observed in the sVCG, recorded by a cubical lead system, with particular reference to the "QRS plane," in a group of normal subjects and suggests a system for classifying abnormalities of the sVCG, based on the QRS plane.

SPATIAL vectorcardiography and the more familiar scalar electrocardiography are 2 different methods of recording the same phenomena. The essential difference between them is that the spatial vectorcardiogram (sVCG) gives a 3-dimensional synthesis of information that is not readily obtainable by the methods of scalar electrocardiography.

If the vectorcardiographic method is to add any new information to the knowledge already acquired from clinical electrocardiography, it is reasonable to assume that it will be found in the inherent 3-dimensional characteristics of the sVCG: the spatial orientation and the contour of the sVCG loops. Definition of the normal vectorcardiogram and departures from normality should take this into account, and should not be limited to the projection of the sVCG on the frontal, sagittal, or transverse planes, which are, after all, chosen quite arbitrarily as far as the heart is concerned.

Vectorcardiographic study of a number of normal subjects and patients with various types of heart disease has led us to the conclusion that the "QRS plane" (Schellong's "plane of the QRS loop,"[17] Rochet and Vastesaeger's "plane of predilection"[15]) is a constant normal finding and provides a useful standard of reference for defining the normal sVCG. This report describes our findings in a group of normal subjects and suggests a classification of sVCG abnormalities based on the "QRS plane."

From the Department of Medicine, The Johns Hopkins University and Hospital, Baltimore, Md.

This investigation was supported by a grant (H-328) from the National Heart Institute, U. S. Public Health Service. Parts of this work were presented at the Second World Congress of Cardiology, Washington, D. C., in September 1954.

Methods

The panoramic vectorcardiograph used in this investigation has been described previously,[12] and allows the observer to view or photograph any projection of the sVCG. This instrument is ideal for the identification of the QRS plane of predilection and departures from it, the only alternative method being construction of wire models of the sVCG.

Figure 1 shows the lead system used for vectorcardiography. Three electrodes lie in a transverse plane passing through the second costosternal junction: (1) on the right anterior thorax, just medial to the anterior axillary line, (2) on the right back, on a sagittal axis passing through electrode 1, (3) on the left back, just medial to the posterior axillary line. A fourth electrode is placed on the right lower back, in such a position that its distance from electrode 2 equals the distance between electrodes 2 and 3, and the axis of electrodes 2 and 4 is at right angles to a line between 2 and 3. No correction factors are applied to the voltages obtained from these leads. This system has been in use in our laboratory since 1950; it was chosen because it provided a bipolar lead system in which the electrodes are roughly equidistant from the anatomic center of the heart. The records obtained by this system are usually very similar to those obtained by other cubical bipolar systems, such as Grishman's[10] but often differ in detail from records obtained in the same patient by the tetrahedral system.[19]

It must be emphasized that the specific measurements in this report apply only to vectorcardiograms recorded by this lead system. Comparison with different lead systems suggests that other generally used systems[5, 10, 19] give similar, although not identical, sVCG's. The principles on which this study is based could be applied to any lead system. The relative merit of different lead systems is a problem that is being investigated in a number of laboratories, and no claim of superiority is made for

the system described here. A "corrected" system such as that developed by Frank[6] is probably to be preferred.

In each subject frontal (xy), sagittal (yz), and transverse (xz) projections of the sVCG were recorded, as well as standard and "unipolar" limb leads, standard precordial "V" leads, and additional unipolar leads from the right chest and the back. In addition, the panoramic unit was used to rotate the sVCG until the closest approximation to a QRS plane could be identified, (fig. 2) and records

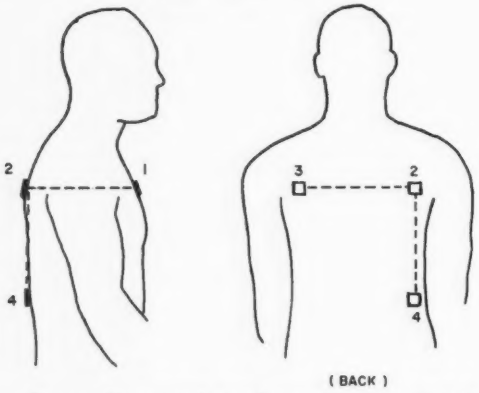


FIG. 1. Vectorcardiographic lead system used in this investigation.

were made of the "edge view," "open view," (defined below) and other projections.

A spatial coordinate system previously described[1] was used to identify the orientation of axes. This coordinate system is analogous to geographic lines of latitude and longitude, with azimuthal values being equivalent to longitude, elevation equivalent to latitude, and the null-point at the center of the globe. Elevation is negative for "northern latitudes," and positive for "southern." In the hemisphere anterior to the null-point azimuth is positive; in the posterior hemisphere, negative. The 0 coordinate is the axis of intersection of the transverse and frontal planes, extending from the null-point toward the patient's left.

Definitions

1. *Axis.* Any line passing through the hypothetical electric null-point. The more anterior end of an axis is used to define its position.

2. *Plane of Predilection of an sÊ-Loop.* The plane in which the ratio of major/minor amplitude is smallest. In practice the QRS plane is located by rotating the sVCG on the oscilloscope screen with the panoramic unit (fig. 2) at elevation = 0°, until the projection with the maximum major/minor amplitude (edge projection) is found.

The term "plane" as applied to the QRS sÊ-loop "cannot be accorded a mathematical rigor."[16] The normal QRS sÊ-loop lies approximately in a plane, and the closeness of the approximation can

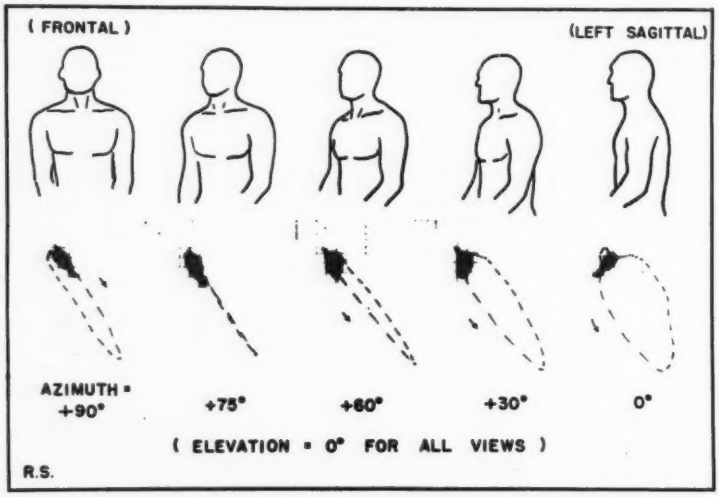


FIG. 2. The 5 projections of the sVCG shown above, identified by the azimuth and elevation of the observer, illustrate the method of locating the QRS plane with the panoramic vectorcardiograph. In this normal subject (age 25 years) the intersection of QRS plane with transverse plane is at azimuth = +75°. The projections shown were displayed on a cathode-ray tube by adjusting the elevation and azimuth controls of the instrument. The outlines of the thorax indicate the approximate anatomic view corresponding to each sVCG projection.

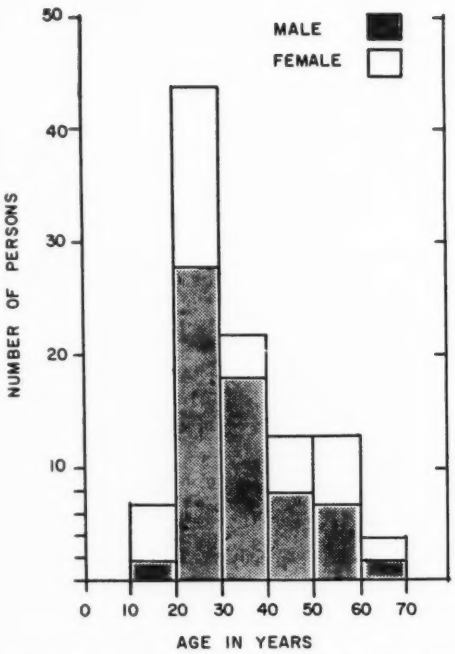


FIG. 3. Age and sex distribution of 103 normal subjects.

be defined by the maximum ratio of major to minor amplitudes.

The plane of an sÊ-loop can be considered to have a cephalad and a caudad surface for descriptive purposes, except when it is perpendicular to the transverse plane. In the latter event the 2 surfaces may be identified as left or right.

Two measurements suffice to determine the position of an sÊ-loop plane: the axis of its intersection with the transverse plane, and the minimum angle between the caudad surface of the sÊ-loop plane and the transverse plane.

3. *Edge Projection.* sVCG projection on a plane perpendicular to the sÊ-loop plane. (The terms "projection" and "view" are used synonymously.)

4. *Open Projection.* sVCG projection on the sÊ-loop plane. When not otherwise specified, "open projection" and "edge projection" refer to the QRS plane.

5. *Maximal Instantaneous Vector of an sÊ-Loop.* This term is self-explanatory, but it should be appreciated that it is not identical with the *mean* vector, e.g., Â QRS, although it often approximates it.

6. *Major Axis.* The axis of the maximal instantaneous vector.

7. *Minor Axis.* An axis perpendicular to the major axis.

8. *Major Amplitude.* Over-all length of the sÊ-loop projected on the major axis (fig. 5).

9. *Minor Amplitude.* Over-all width of the sÊ-loop projected on the minor axis (fig. 5).

10. The angle between an sÊ-loop plane and an axis not in the plane is defined as the angle subtended by the axis and the line of intersection between the sÊ-loop plane and a plane perpendicular to it, passing through the axis. The minimum angle between the QRS plane and the maximal T vector is an example.

Subjects

A total of 103 subjects was studied, including physicians and technicians of the hospital staff, and hospital patients with no historic or clinical evidence of heart disease or other disease known to affect the electrocardiogram. The age and sex distribution in this "normal" group is shown in figure 3. No effort was made to secure a statistical cross-section of the populace, and the group is heavily weighted in the third and fourth decades. Complete panoramic study was carried out in 59 of these subjects, with an age and sex distribution similar to that of the total group.

Our observations on the abnormal sVCG are based on study of more than 600 patients with heart disease of various kinds. Detailed panoramic investigation of the QRS plane was made in 92 of these cases.

RESULTS

Normal sVCG

Measurements on the sVCGs of normal subjects are summarized in table 1. In each case explored with the panoramic unit a QRS plane could be identified, and the edge view of the QRS sÊ-loop had a major/minor amplitude ratio of at least 8/1 (average, 14/1). The average orientation of the QRS plane and its range of variation are illustrated in figure 4. The average intersection of QRS plane and transverse plane was azimuth +65°, with a range from +5° to 135°.

The acute angle between the cephalad surface of the transverse plane and the relatively caudad surface of the QRS plane always lay toward the patient's right, and ranged from 22° to 80°, with a mean of 51°.

In the open projection on the caudad surface of the QRS plane the direction of QRS rotation was invariably clockwise. The contour of the QRS loop in this projection was surprisingly similar in all patients, although many indi-

TABLE 1.—*Measurements of Normal Spatial Vectorcardiograms*

Measurement	Projection			
	59 Cases	103 Cases		
	Open	Frontal	Right sagittal	Transverse
Maximum QRS vector: direction (°)	+90*	+51 (+6 to +95)	+117 (+85 to +170)	−33 (−106, 0, +10)
Major QRS amplitude (mv.)	1.18 (0.87 to 1.95)	1.15 (0.51 to 2.20)	1.01 (0.30 to 2.15)	0.86 (0.20 to 2.10)
Ratio: major/minor amplitude	3.37 (1.1 to 7.0)	4.8 (0.9 to >8.0)	4.0 (1.0 to >8.0)	1.8 (0.8 to 6.5)
QRS rotation: (% of cases)†				
Clockwise	100	67	95	0
Counterclockwise	0	8	0	98
Figure-8	0	18	3	2
Linear	0	7	2	0
10 msec. QRS vector: direction (°)	−24 (−55 to −10)	−137 (−170, 0, +175)	−26 (−70, 0, +88)	+118 (+4 to +150)
P sÊ-loop: maximum vector: direction (°)	+85 (+62 to +91)	+42 (−2, 0, +90)	+114 (−2, 0, 180)	−23 (−71, 0, +30)
T sÊ-loop: maximum vector: direction (°)	+71 (+60 to +92)	+45 (0 to +70)	+88 (0 to +160)	−2 (−40, 0, +38)
Angle between maximum QRS and T vectors (°)	19 (0 to 30)	17 (0 to 94)	33 (2 to 170)	25 (0 to 122)

Values given are means, with range of observed values in parentheses. Where the range includes both positive and negative values, either 0° or 180° is listed between the extremes, to indicate which segment of the coordinate system is included. For example, (−2, 0, 180) means that the range includes negative values between 0° and −2°, and positive values between 0° and 180°.

The open projection is viewed on the caudad or rightward surface of the QRS plane.

* In the open projection the coordinate system is determined by the maximum QRS vector, which is arbitrarily placed at +90°.

† Rotation is termed "figure-8" only if both loops of the "8" have a major amplitude equal to at least one-fourth the major amplitude of the whole QRS loop in the same projection. "linear" indicates that the major/minor amplitude ratio is 8/1 or more.

vidual variations were present. As reported by others,[5; 10, 16, 17] the normal QRS sÊ-loop describes a fairly smooth elliptical curve. Small irregularities in the curve (Schellong's "ein- und ausbuchtung") are not unusual in normal records when the frequency response of the apparatus extends to 100 c.p.s. or more, but sharp reversals of direction were not seen. Measurements of the major and minor amplitudes, and other characteristics of the sVCG in this projection, are summarized in table 1, and shown diagrammatically in figure 5. A typical normal sVCG is shown in figure 6. Figure 8 shows an sVCG from a normal subject with counterclockwise frontal QRS rotation, which is less frequently seen.

As pointed out by Schellong (p. 42)[17] and others, the direction of rotation of the QRS loop in the frontal plane is related to the orientation of the QRS plane. When the QRS plane-transverse plane intersection was between +5° and +75°, the frontal plane QRS loop rotation was usually clockwise. When it lay between +75° and +90°, the frontal plane QRS loop was narrow and often "figure-8" in contour. When it was +90° to +135°, the frontal plane QRS rotation was usually counterclockwise (fig. 7).

The T sÊ-loop usually lay in almost the same plane as the QRS sÊ-loop, with the maximal T vector slightly cephalad to the QRS plane. The minimum angle between the maximal T

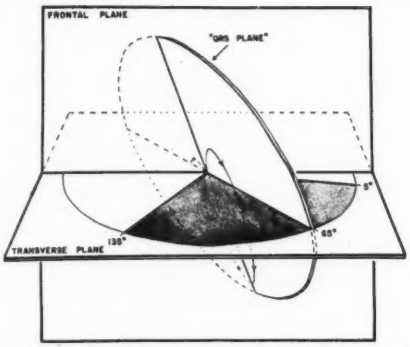


FIG. 4. Average orientation of the normal QRS plane, and its range of variability.

vector and the QRS plane* averaged 3° cephalad of the QRS plane, and ranged from 17° cephalad to 13° caudad.

The angle between the maximal QRS and T vectors in the open projection averaged 19°, with the maximal T vector anterior to the maximal QRS vector. The variations in position of the maximal T vector observed in this projection ranged from 2° on the posterior side of the maximal QRS vector to 30° anterior to it.

The orientation of the P sÊ-loop showed relatively little variation in all projections. The minimum angle between the maximal P vector and the QRS plane was usually less than 5°, caudad or cephalad.

The plane of predilection of the P and T sÊ-loops was not studied in detail.

DISCUSSION

Schellong[17] first reported the observation that the normal QRS sÊ-loop lies approximately in a single plane, and Rochet and Vastesaeger later described the normal QRS plane and its physiologic variations in some detail.[16] Our observations confirm in general the descriptions of these investigators, and give them a quantitative expression.

The most valuable characteristic of the

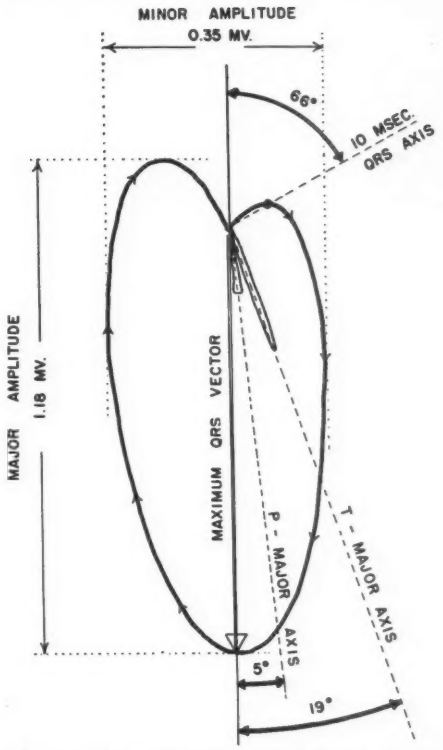


FIG. 5. Diagrammatic representation of normal open projection sVCG, with average measurements from 59 normal subjects.

open projection of the sVCG in the QRS plane is the relatively narrow range of normal variation in this projection, in comparison with the usual frontal, sagittal, or transverse projection.

Variations in the 10-msec. QRS vector in the open projection, for example, were limited to a range of 45° (−10° to −55°) while in the frontal plane projection its normal range covers almost 360°. The angle between maximal QRS and T vectors is another example; its range in the open projection is considerably less than that reported for the frontal plane[8] or for the spatial QRS-T angle.[18]

There is a systematic difference between our findings in normal subjects and those of Burch, Abildskov, and Cronvich,[4] in that their maximal QRS vectors in the sagittal projection generally lie more anterior than ours. Comparison of different lead systems indicates that this

* This minimum angle is not necessarily the angle between maximal QRS and T vectors observed in an edge projection of elevation = 0°. Exploration of the edge projection at other elevations is necessary to determine the true minimum angle (see definitions, item 10).

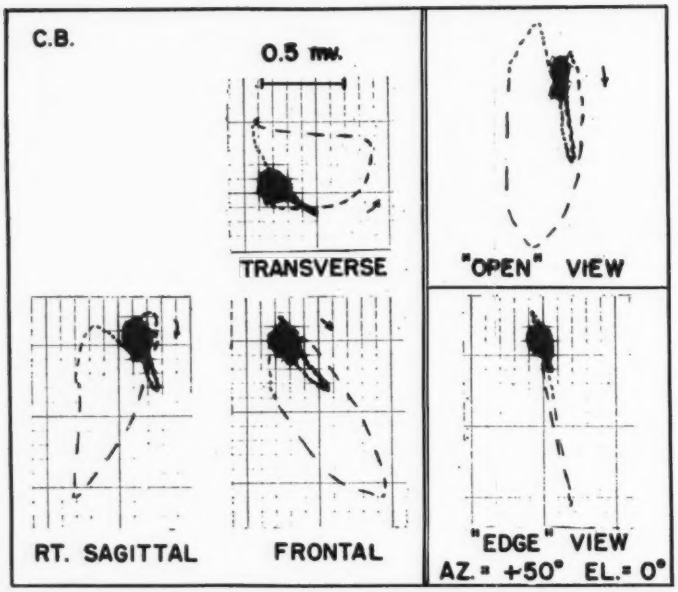


FIG. 6. Normal male, age 30 years. In this and subsequent figures, the VCG timing dashes are 2.5 milliseconds apart, and the mounting of frontal, sagittal, and transverse projections follows the recommendations of the American Heart Association.[3]

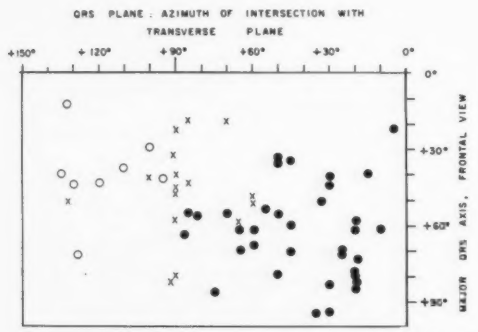


FIG. 7. Relation between orientation of QRS plane, frontal plane major QRS axis (or maximal QRS vector), and frontal plane QRS rotation. (●) = clockwise QRS rotation in frontal plane; (×) = "figure-8"; (○) = counterclockwise.

is an essential difference between cubical and tetrahedral lead systems. The division of normal records into "Type 1" (elliptical) and "Type 2" (more circular and more posterior) described by the New Orleans group[1, 4] has not been apparent in our series. It is of interest that comparison of records from the equilateral tetrahedron and from a "corrected" lead system has shown more uniformity among normal subjects with the latter.[2]

Significance of the QRS Plane

The existence of a QRS plane in the sVCG of normal subjects is in itself somewhat surprising. Considering the diverse paths along which the ventricular muscle is activated, and the widely separated muscle fibers that are activated simultaneously, one would hardly expect *a priori* that the successive vector sums of these separate events would lie in the same plane. The possibility that this apparent plane is an artifact imposed by the conducting materials between the heart and our electrodes should not be ignored, but observations on the isolated rabbit heart in a homogeneous fluid medium in our laboratory show that the QRS plane is still present under these conditions.

The normal orientation of the QRS plane roughly parallels that of the interventricular septum, and it is tempting to assume that individual differences in orientation of the plane reflect individual differences in the anatomic

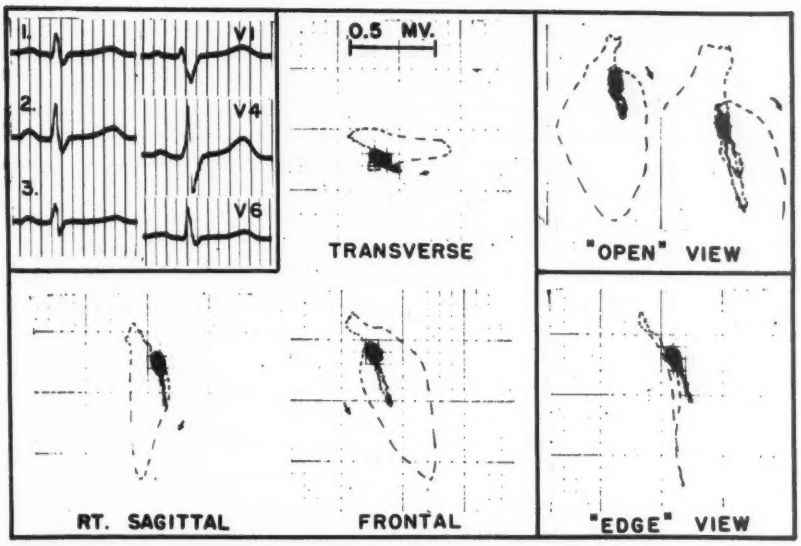


FIG. 8. Normal subject, male, age 34 years, showing counterclockwise QRS rotation in the frontal projection, a relatively rare finding. The edge projection was found at azimuth +135°. In this and subsequent illustrations the heavy vertical time lines of the electrocardiogram represent intervals of 0.1 second.

position of the heart, but there is no direct evidence for this assumption.

It is easy to demonstrate by wire models or diagrams that rotation of the QRS plane can explain much of the variability of the conventional scalar electrocardiographic leads in normal subjects, as Gardberg and Ashman,[7] Jouve (p. 104),[11] Wolff,[20] and others have done. This demonstration by no means proves, however, that such rotations in the QRS plane are related to corresponding variations in the *anatomic* position of the heart. In the present study, the normal variations in orientation of the QRS plane seem to be considerably greater than could be explained by variation in heart position.

The autopsy studies of Grant[9] provide strong evidence that the rotation of the heart about an anterior-posterior axis varies less than 45° in different subjects, and that very little rotation around the longitudinal axis of the heart occurs. He pointed out that the extreme longitudinal axis rotations described in electrocardiography have simply been assumed as convenient explanations of certain electrocardiographic findings, without supporting anatomic evidence. We are in complete accord with his views on this point, and believe they are amply confirmed by routine roentgenography and angiocardiography. It seems much more likely that the position of the QRS plane varies in normal subjects principally because of normal variations in the structure of the ventricles and the sequence of myocardial activation.

Relation between Orientation of the QRS Plane and the Maximal QRS Vector

Our results do not show a close correlation between the orientation of the QRS plane and the frontal plane maximal QRS vector. Rochet and Vastesaeger[15, 16] reported that a mean frontal QRS axis of 0° to about +30° was usually accompanied by a QRS plane very near the frontal plane, and counterclockwise QRS rotation in the frontal projection. Mean QRS axes more rightward than +60°, according to these authors, were correlated with a nearly sagittal QRS plane, and clockwise QRS rotation in the frontal plane, while mean QRS axes in the neighborhood of +45° were associated with narrow or figure-8 frontal plane QRS

loops. Gardberg and Ashman[7] reached similar conclusions.

Figure 7 shows that our data do not support this generalization. The direction of rotation of the QRS sÊ-loop in the frontal projection is definitely related to the orientation of the QRS plane: clockwise rotation is found only when the QRS plane falls between 0° and +90°, counterclockwise rotation when it lies beyond +90°, and figure-8 contours when it is in the neighborhood of +90°. There is only a slight relationship, however, between the orientation of the QRS plane and the maximal QRS vector in the frontal projection: clockwise, counterclockwise, and figure-8 rotations are found throughout the range of maximal frontal QRS vectors.

It is of interest that attempts to reconstruct the spatial QRS loop from routine electrocardiograms led Gardberg and Ashman,[7] and more recently Peñaloza and Tranchesi[14] to conclude that frontal QRS rotation is usually *counterclockwise* in the normal subject, while in our investigations, as well as those of Grishman and Scherlis,[10] and Burch, Adildskov, and Cronvich,[4] it was clockwise in the majority of instances.

Abnormal sVCG

The relative constancy of the QRS loop contour within its own plane, in spite of variations in QRS plane orientation, is a convenient basis for classifying abnormalities of the sVCG. The following classification lists the possible departures from normality: (1) the QRS plane may be displaced beyond its normal

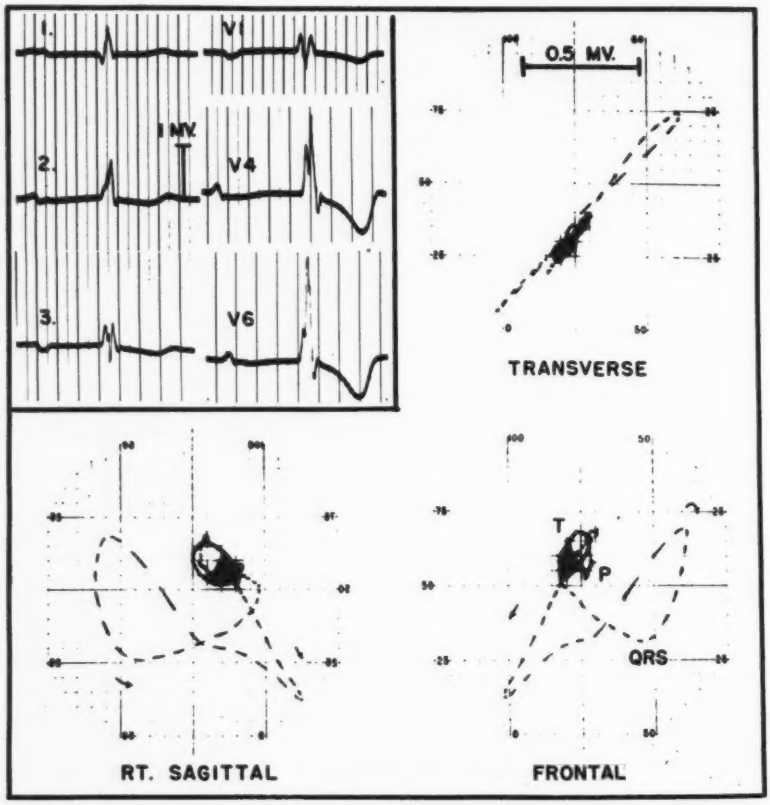


FIG. 9. Female, age 37 years, with rheumatic mitral stenosis. An example of the second class of sVCG abnormality, with the QRS sE-loop in a plane, but a distorted QRS contour within the plane. QRS duration = 0.09 second. The P-R interval is prolonged.

range, (2) the QRS contour may become abnormal within its plane, or (3) the plane itself may be bent or otherwise distorted. P and T loop abnormalities could be classified in the same way, and a final category added to include abnormal relations between P, QRS, and T loops, e.g., abnormalities of the angle between QRS major axis and T major axis.

The first type is frequently seen in the early stages of left or right ventricular hypertrophy, and is the spatial analog of right and left axis deviation in the standard electrocardiogram. With early right ventricular hypertrophy, for example, the QRS plane tilts to bring the maximal QRS vector rightward and anteriorly. With mild degrees of hypertrophy the QRS contour may be normal and continue to lie in a plane, but in later stages bending of the QRS plane appears.

An example of the second type, in which the QRS contour is abnormal within its plane, is shown in figure 9. In this instance the QRS contour is radically distorted, as seen in the frontal and sagittal projections, but in spite of the meandering contour in these projections the whole QRS loop lies approximately in a single plane, which happens to present an edge projection in the standard transverse projection.

In the third type, where the QRS loop is distorted so that it no longer lies in a plane, any degree of distortion may occur from simple bending of the original plane to very complex patterns in which no semblance of a plane can be found.

The example in figure 10 shows a relatively simple longitudinal folding of the plane. One cannot really speak of an "edge" or "open" projection in this situation but if we view the loop from a position a little anterior to the transverse view (azimuth = $+90°$, elevation = $-70°$) it can be seen that at least the first half of the QRS complex lies in a plane, while its later portions have been bent forward. An approximate open projection is found at azimuth = $+105°$, elevation = $50°$, in which the terminal appendage is foreshortened. The electrocardiogram shows the pattern of right bundle-branch block, and the late portion of the QRS loop, which is bent forward, corresponds to the slow S_1 and R-V_1 of the scalar electrocardiogram.

A similar case, but with the early QRS loop displaced to the left and upward, has been published elsewhere.[13]

Longitudinal twisting of the QRS plane is another variety of distortion, as illustrated in figure 11. This case, with the electrocardio-

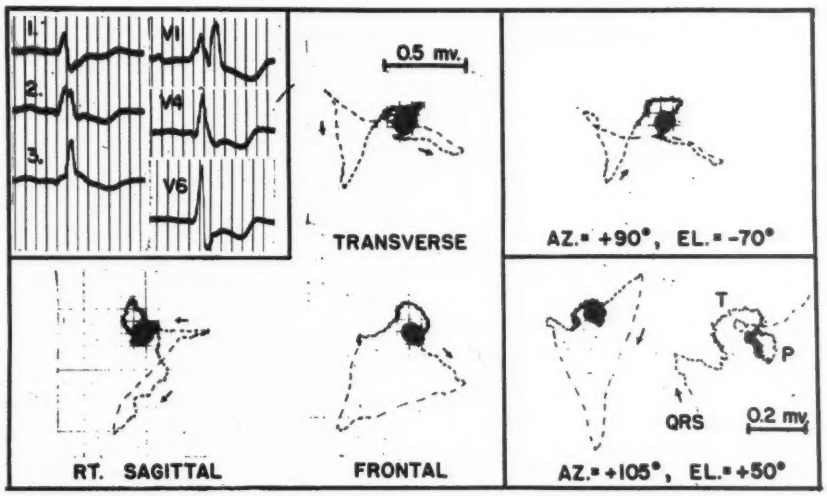


FIG. 10. Female, age 67 years, with arteriosclerotic heart disease. An example of relatively simple distortion of the QRS plane, with folding along the major axis. QRS duration = 0.14 second and electrocardiographic pattern of right bundle-branch block.

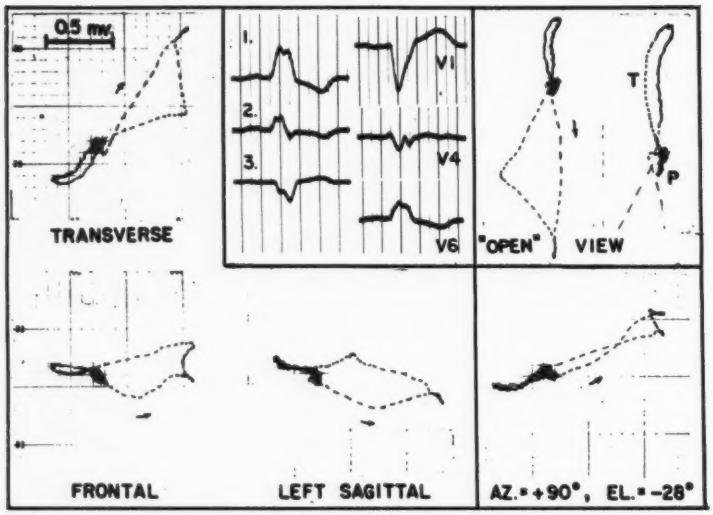


FIG. 11. Male, age 55 years, with angina pectoris and arteriosclerotic heart disease. Somewhat more distortion of the QRS plane with twisting around the major axis, and abnormal contour. The projection at azimuth = +90°, elevation = −28°, is the closest approximation to an edge projection. QRS duration = 0.130 second, with electrocardiographic pattern of left bundle-branch block.

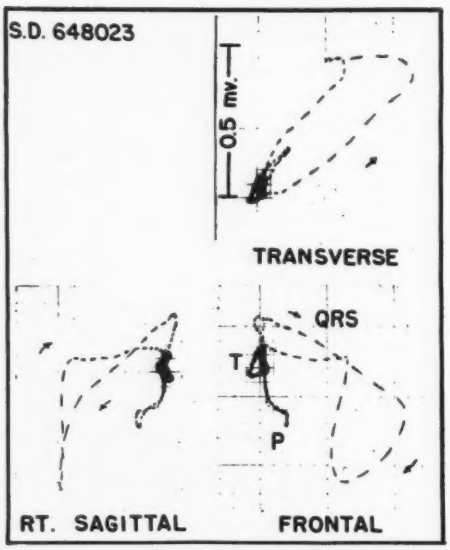


FIG. 12. Complex distortion of the QRS plane, in a patient aged 48 years, with a history of myocardial infarction and electrocardiographic signs of old anterior myocardial infarction. The QRS voltage is reduced, so that the P sÊ-loop looks relatively big.

graphic pattern of left bundle-branch block, shows displacement of the QRS loop to the left, and longitudinal twisting of the loop best seen from a viewpoint slightly above the standard frontal position (azimuth = +90°, elevation = −28°). The closest approximation to an open view shows a distorted triangular contour, with a curious bowing of the distal limb of the triangle.

Finally, the QRS contour may be radically distorted, with multiple bends and twists, as in figure 12. In this instance, there was a clear history of previous myocardial infarction, and the scalar electrocardiogram showed signs of an old anterior myocardial infarction.

This proposed classification cuts across the conventional categories of clinical electrocardiographic diagnosis, as well as the etiologic types of heart disease. Myocardial infarction, for example, may destroy the QRS plane as in figure 12, but it may also produce simple displacement of the plane, changes in contour only, or no chronic abnormality at all. Cases with the electrocardiographic pattern of right ventricular hypertrophy may have vectorcardiograms of any one of the 3 major types described.

This is not necessarily a disadvantage, and might be expected if the classification reflects underlying abnormalities of structure and function not yet clearly recognized. It is impossible to evaluate the significance of these

different types of abnormality until the significance of the normal QRS plane and its relation to the detailed spread of activation in the myocardium is clarified.

For the present, this concept at least offers a way of thinking about the normal spatial vectorcardiogram and departures from normality that is based on the vectorcardiogram itself and not on preconceived ideas borrowed from scalar electrocardiography.

Summary

A quantitative study of the characteristics of the normal spatial vectorcardiogram (sVCG) was carried out on 103 normal subjects. The normal limits so determined apply only to the specific cubical lead system employed, but the principles can be applied to any lead system. In 59 of these normal subjects the panoramic vectorcardiograph was used for systematic exploration of the sVCG. In each case the QRS sÊ-loop lay approximately in a plane, so that an edge projection with a major/minor axis amplitude ratio of 8/1 or more could be found.

The orientation of the QRS plane varied considerably, but the contour of the QRS sÊ-loop within the plane was relatively constant. The normal limits of the sVCG projected on the QRS plane were narrower than in the conventional frontal, sagittal, or transverse projections.

A classification of vectorcardiographic abnormalities is proposed, based on the normal QRS plane. This classification emphasizes the 3-dimensional nature of the sVCG, without reference to conventional scalar electrocardiography.

Acknowledgment

The assistance of Dr. Charles A. Bertrand in this work, while a Public Health Service Research Fellow of the National Heart Institute, is acknowledged with gratitude. We are also indebted to Mrs. Richard Hess and Miss Kate Fleenor for their excellent technical help, and to the many physicians and technicians of the hospital staff who were persuaded to volunteer as normal subjects.

Summario in Interlingua

Un studio quantitative del characteristicas del normal vectocardiogramma spatial (VCGs) esseva effectuate super le base de observationes in 103 individuos. Le limites del manifestationes normal que esseva assi determinate es applicabile solmente al systema de derivation cubical (i.e. le systema usate in iste studio), sed le principios es equalmente applicabile a non importa qual altere systema de derivation.

In 59 del 103 subjectos normal le vectocardiographo panoramic esseva usate pro le exploration systematic del VCGs. In omne casos le spira sÊ de QRS jaceva approximativemente in un plano de maniera que un projection angular poteva esser trovate con un proportion de al minus 8 a 1 inter major e minor amplitude axial.

Le orientation del plano QRS variava considerabilemente, sed le contorno del spira sÊ de QRS intra le plano esseva relativemente constante. Le limites normal del VCGs projicite super le plano QRS esseva minus late que in le projectiones conventional frontal, sagittal, e transverse.

Es proponite un classification de anormalitates vectocardiographic, basate super le plano QRS normal. Iste classification sublinea le natura tridimensional del VCGs sin referentia al electrocardiographia scalar conventional.

REFERENCES

[1] Abildskov, J. A.: A study of the spatial vectorcardiogram in normal subjects over the age of forty years. Circulation **12:** 286, 1955.

[2] —, and Pence, E. D.: A comparative study of spatial vectorcardiograms obtained with the equilateral tetrahedron and a "corrected" system of electrode placement. Circulation **13:** 263, 1956.

[3] American Heart Association Committee on Electrocardiography. Recommendations for standardization of electrocardiographic and vectorcardiographic leads. Circulation **10:** 564, 1954.

[4] Burch, G. E., Abildskov, J. A., and Cronvich, J. A.: Studies of the spatial vectorcardiogram in normal man. Circulation **7:** 558, 1953.

[5] Duchosal, P. W., and Sulzer, R.: La vectocardiographie. Basel, S. Karger, 1949.

[6] Frank, E.: An accurate, clinically practical system for spatial vectorcardiography. Circulation **13:** 737, 1956.

[7] Gardberg, M., and Ashman, R.: The QRS complex of the electrocardiogram. Arch. Int. Med. **72:** 210, 1943.

[8] Grant, R. P., and Estes, E. H.: Spatial Vector Electrocardiography. Philadelphia, Blakiston, 1951.

[9] —: The relation between the anatomic position of the heart and the electrocardiogram. A criticism of "unipolar" electrocardiography. Circulation **7:** 890, 1953.

[10] Grishman, A., and Scherlis, L.: Spatial vectorcardiography. Philadelphia, W. B. Saunders Co., 1952.

[11] Jouve, A., Buisson, P., Albovy, A., Velasque, P., and Bergier, G.: La vectocardiographie en clinique. Paris, Masson et Cie, 1950.

[12] Milnor, W. R., Talbot, S. A., and Newman, E. V.: A study of the relationship between unipolar leads and spatial vectorcardiograms, using the panoramic vectorcardiograph. Circulation **7:** 545, 1953.

[13] —, and Bertrand, C. A.: The electrocardiogram in atrial septal defect. A study of 24 cases, with observations on the RSR′-V_1 pattern. Am. J. Med. 1957. In press.

[14] Peñaloza, D., and Tranchesi, J.: The three main vectors of the ventricular activation process in the normal human heart. I. Its significance. Am. Heart J. **49:** 51, 1955.

[15] Rochet, J., and Vastesaeger, M. M.: La variation de la valeur manifeste et de l'angle α pendant la cycle cardiaque normal chez l'homme. Arch. internat. de physiol. **49:** 113, 1939.

[16] Vastesaeger, M. M.: Les troubles de la conduction intraventriculaire chez l'homme. Acta cardiol. Supplement 1, 1946.

[17] Schellong, F.: Grundzuge einer klinischen Vektordiagraphie des Herzens. Berlin, Springer, 1939.

[18] Simonson, E., and Keys, A.: The spatial QRS and T vector in 178 normal middle-aged men. Circulation **9:** 105, 1954.

[19] Wilson, F.: The substitution of a tetrahedron for the Einthoven triangle. Am. Heart J. **33:** 594, 1947.

[20] Wolff, L., Richman, J. L., and Soffe, A. M.: The effect of heart position and rotation on the cardiac vector: an experimental study. Am. Heart J. **47:** 161, 1954.

Johnson, S. R., and Svanborg, A.: Investigations with Regard to the Pathogenesis of So-called Fat Embolism. Serum Lipids and Tissue Esterase Activity and the Frequency of So-called Fat Embolism in Soft Tissue Trauma and Fractures. Ann. Surg. **144:** 145 (Aug.), 1956.

The authors presented various observations in the literature to refute the view that in fat embolism the emboli consist of mechanically released particles of fat, usually marrow fat from fractured bones. They also presented experimental evidence against such a hypothesis. In one series of rabbits a hind leg was crushed by means of a blunt instrument without perforation of the skin, while in another the hind limb was ligated for 1 to 2 hours. In most of the animals in both series an increase of the lipid content in serum was noted, which was considered to be the result of the injuries. However, no definite change in esterase activity could be observed. Fat droplets were demonstrated in the capillaries using Sudan III. The authors concluded that accumulations of droplets of fat in the tissue capillaries, of the type commonly considered pathognomonic of so-called fat embolism, occur as frequently in connection with injuries to soft tissue as in the case of fractures with injuries of the marrow. They were unable to cast any light on the cause for the increase in content of lipid of the serum after trauma.

Abramson

Syncope as an Indication of Digitalis Toxicity

By Sol Glotzer, M.D.

Increased sensitivity of the carotid sinus to stimulation is known to accompany digitalis toxicity. Syncope induced by deglutition as a manifestation of this hypersensitivity is exceedingly unusual and warrants description.

TOXIC reactions to digitalis are familiar to all who treat cardiac disease, but occasionally an unusual reaction is seen that does not at first seem related, and only in the light of later events becomes obvious as a greater than ordinary degree of toxicity. Such a situation is reported here.

Case Report

A. H., a 77-year-old woman, was admitted to the Williamsburgh General Hospital on October 5, 1955, with a history of left radical mastectomy for malignant disease 15 years previously with no recurrence to date. Hypertension was of many years' duration. She had shown slight evidences of congestive heart failure some months prior to admission, had been digitalized, and was comfortable on a maintenance dose of 0.2 mg. of digitoxin for a while. Beginning in July 1955 she had noted mild dysphagia, with a feeling of a "lump" behind the sternum after swallowing. For 11 days prior to admission syncope occurred immediately after swallowing water, but not after food. Each episode was manifested by pallor, cyanosis, loss of consciousness, and mild convulsive movements, lasting for a short time.

On admission, blood pressure was 200/110, the heart was enlarged, regular, with occasional extrasystoles, and a loud musical murmur was heard at the apex, extending upward over the aortic area. No signs of congestive failure were present. X-ray of the esophagus was normal, and calcification was seen in the abdominal aorta.

The electrocardiogram showed left axis deviation, with the "hinge-door" depression of S-T segments indicative of digitalis effect. Q waves in leads II, III, and aV_F suggested old damage of the posterior wall of the myocardium (fig. 1).

Pressure on the right carotid sinus induced a typical syncopal attack with cardiac arrest and nodal escape. The patient was given a swallow of cold water on 2 separate occasions, and each time she lost consciousness, with a fall in blood pressure to zero, sinus arrest, and nodal or ventricular escape. Each episode, whether induced by swallowing or by carotid sinus pressure, was identical.

From the Williamsburgh General Hospital, Brooklyn, N. Y.

Digitalis was discontinued, and potassium chloride, 2 Gm. daily, was given. After 2 days she was able to swallow liquids with no distress and carotid pressure no longer caused syncope.

Discussion

The carotid sinus is supplied by the nerve of Hering, which joins the glossopharyngeal nerve and communicates with the vagus. Pressure on the right sinus thus decreases the activity of the sinoatrial node and slows the heart.

Sensitivity of the carotid sinus is increased in a variety of conditions, particularly in myocardial infarction,[1] congestive heart failure,[2] and arteriosclerotic hypertensive vascular disease.[3] Digitalis in excess also causes sinus bradycardia or arrest, in addition to the more familiar effects, i.e., ectopic beats, atrial tachycardia, and atrioventricular block. Sensitivity of the sinus can be increased by the administration of as little as 3 gr. of digitalis folia.[2] In our patient such an increase apparently was enough to permit only the slightest vagal stimulation to cause cardiac arrest, the stimulus probably arising from rapid distention of the lower esophagus. We presume that the reason a swallow of water precipitated an attack whereas solid food did not is related to the speed of descent of the ingested material and therefore to the speed of distention. Another suggestion is that the sinus is excited by the pull exerted on the sinus wall during deglutition, either by the cervical musculature, or by the actual passage of food through the esophagus.[4] That digitalis was implicated in this mechanism may be inferred by the complete disappearance of the symptom complex after discontinuance of the drug.

The association between digitalis and syncope may be purely coincidence, but it was striking enough to be suggestive. Proof of the

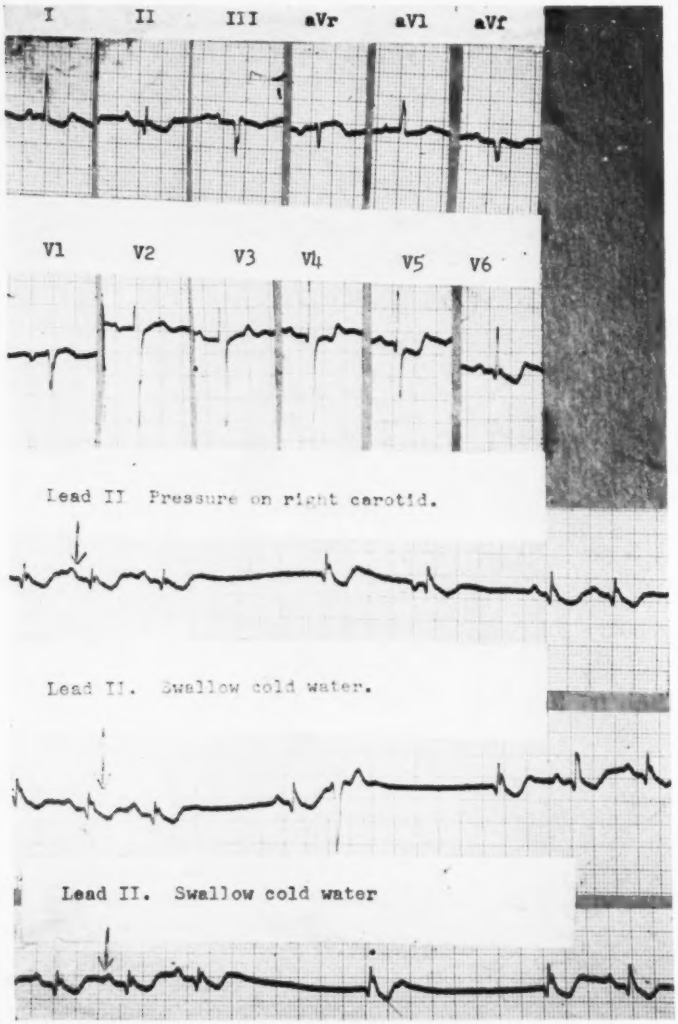


FIG. 1. Electrocardiogram showing depression of sinoatrial pace-maker on right carotid pressure and swallowing cold water.

association, by again administering digitalis to the point of toxicity, seemed too hazardous to attempt.

SUMMARY

This report presents a patient with hypertensive arteriosclerotic heart disease, in whom attacks of syncope were induced by swallowing water but not solid food. The cause was traced to increased carotid sinus sensitivity resulting from digitalis toxicity, and no further episodes appeared after digitalis was discontinued. The possibility exists of a purely coincidental relationship between syncope and digitalis toxicity, but, even in the absence of proof by repetition, the association is very suggestive.

SUMMARIO IN INTERLINGUA

Es reportate le caso de un patiente con morbo cardiac arteriosclerotic hypertensive in qui

attaccos syncopic esseva inducite per le inglutition de aqua sed non de alimentos solide. Le causa esseva trovate in un augmentate sensibilitate del sinus carotic resultante ab toxicitate per digitalis. Nulle episodios additional de syncope occurreva quando le uso de digitalis esseva cessate. Il remane possibile que il se tracta in iste caso de coincidentia, sed mesmo in le absentia de provas per repetition, le association de syncope con toxicitate per digitalis es multo plausibile.

REFERENCES

1 Sigler, L. H.: Clinical observations on carotid sinus reflex. Am. J. M. Sc. **186:** 118, 1933.

2 Nichol, A. D., and Strauss, H.: The effects of digitalis, urginin, congestive heart failure and atropine on the hyperactive carotid sinus. Am. Heart J. **25:** 746, 1943.

3 Weiss, S., Ferris, E. B., and Capps, R. B.: Carotid sinus syncope. Medicine **14:** 377, 1935.

4 Adamson, C. A., Ekstrand, R., Hook, O., and Lindblom, Y.: A contribution to the treatment of the carotid sinus syndrome. Acta med. scandinav. **153:** 355, 1956.

Kaufman, H. E., and Rosen, S. W.: Clinical Acid-Base Regulation—The Bronsted Schema. Surg., Gynec. & Obst. **103:** 101 (July), 1956.

According to the Bronsted theory, an acid is a hydrogen ion donor and a base a hydrogen ion acceptor. In this simple framework, mechanisms of normal and deranged acid-base physiology have been sketched. Renal function in acid-base balance has been considered and the role of carbonic anhydrase in proton excretion has been emphasized. Carbon dioxide transport has also been examined; the role of hemoglobin in this process and the concomitant electrolyte shifts are easily understood in terms of the Bronsted theory. It is in the realm of clinically deranged acid-base balance, however, that the Bronsted theory appears most valuable. A number of pathologic conditions have been discussed and, in all, this theory seems to lend clarity and simplicity. In acidosis, blood hydrogen ion concentration increases. Renal compensation for this increase in hydrogen ion is by liberation of bicarbonate into the blood with concomitant excretion of protons —as ammonium ions and as dihydrogen phosphate ions—in an acid urine. This proton excretion mechanism occurs, whether renal sodium ion excretion is increased, as in acid-gaining acidosis, or decreased, as in respiratory, or in base-losing acidosis. This mechanism applies whether serum sodium is decreased, as in acid-gaining acidosis and base-losing acidosis or increased, as may occur in respiratory acidosis. In alkalosis, the normal kidney conserves acid by failing to excrete ammonium ion and by excreting monohydrogen phosphate rather than forming the more highly protonated dihydrogen phosphate. The kidney can also excrete base as bicarbonate and possibly tricarboxylates. Renal compensation for alkalosis is thus simply conservation of acid and excretion of base.

The unity inherent in the Bronsted theory seems to afford a simple and precise presentation of the mechanisms of acid-base balance. Once the primary hydrogen ion regulation is understood, the electrolyte alterations become apparent from the requirements of electroneutrality.

Maxwell

CLINICAL CONFERENCE

EDITOR: EDGAR V. ALLEN, M.D.
Associate Editor: RAYMOND D. PRUITT, M.D.

Radioactive Iodine Treatment of Angina Pectoris and Congestive Heart Failure

By HERRMAN L. BLUMGART, M.D., A. STONE FREEDBERG, M.D., AND GEORGE S. KURLAND, M.D.

DR. HERRMAN L. BLUMGART: The purpose of this conference is to review a decade of experience in the treatment of intractable heart disease with radioactive iodine. By inducing hypothyroidism, the systemic circulatory requirements are reduced so that they may be within the limits of cardiac reserve. Following the induction of hypothyroidism or myxedema, each patient is maintained at the lowest level of metabolism consistent with comfort. In all our patients, small daily doses of thyroid, 6 to 30 mg. daily, are administered.

We believe that the radioiodine treatment of angina pectoris and congestive failure is necessary only for that small group of patients, probably less than 5 per cent, who remain disabled and in great discomfort despite all standard methods of therapy. For these patients with severe angina pectoris, various surgical methods have been advocated, such as pericardial injury, sympathectomy, posterior rhizotomy, omentopexy, pericoronary neurectomy, or arterialization of the coronary sinus. The radioactive iodine treatment of heart disease obviates the risk and discomfort attendant on surgery.

CASE 1

Mr. W. T. was admitted to the Beth Israel Hospital on May 14, 1955, for evaluation of his angina pectoris and consideration of possible radioactive iodine treatment. He was referred by Dr. Paul D. White, who had seen the patient in 1944 and repeatedly since that time. The patient was 66 years of age. He stated that he had first become aware of his heart disease in 1928, at the age of 39, when he experienced a severe episode of substernal pain radiating to both shoulders and down both arms necessitating bed rest for 6 weeks. A diagnosis of acute myocardial infarction was made. He then experienced little discomfort until 1938 when, at the age of 49, he had a similar episode again interpreted as acute myocardial infarction. Following this episode he began to have fairly frequent attacks of substernal pain radiating to both shoulders on exertion and often radiating down the left arm to the fingertips and through to the back. These attacks occurred particularly while walking in cold weather, after eating, and during the night, waking him from sleep. The patient stated that in 1942, 1945, and 1948, additional episodes of severe cardiac pain occurred accompanied by electrocardiographic changes, elevated temperature, and sedimentation rate, and that each was treated with 6 weeks of bed rest.

In 1951 he was placed on a rigid "rice diet" and experienced improvement in that the anginal attacks were less frequent and less severe. During the year 1954 to 1955, preceding his first admission to the Beth Israel Hospital, despite faithful adherence to the rice regimen, the patient continued to have such frequent attacks of severe angina that he was incapacitated and unable to attend business. He had received various xanthine preparations, pentaerythrityl tetranitrate, and other medications without discernible benefit. Although nitroglycerin alleviated the attacks, frequently well over 100 tablets were taken over a 24-hour period. Oxygen was also helpful and was administered for hours at a time each day. The pains increased in severity and frequency until he was confined to bed and required meperidine for relief of pain at 2- to 3-hour intervals and constant nursing and medical care. Anginal pains of great intensity followed the slightest exertion, meals, any controversy, prolonged conversation, dreams, unusual noises, etc.

On physical examination, the blood pressure in both arms was 120/80. The thyroid gland was not enlarged. Examination of the heart revealed regular rhythm and no enlargement, the aortic second sound was slightly louder than the pulmonic second sound,

From the Department of Medicine, Harvard Medical School, and the Medical Service and Yamins Research Laboratories of the Beth Israel Hospital, Boston, Mass.

This work was supported by the Atomic Energy Commission.

the heart sounds were of good quality, and there were no significant murmurs. The physical examination revealed otherwise normal findings. Laboratory examinations of the blood and urine revealed normal findings. The serum cholesterol was 250 mg. per 100 ml. Serum protein-bound iodine was 5 μg. per 100 ml. Two determinations of the basal metabolic rate were −13 and −24 per cent. On x-ray the heart was normal in size and shape. The radioactive iodine uptake by the thyroid gland 24 hours after a tracer dose was 60 per cent. The electrocardiogram showed no abnormalities except that the T waves in the chest leads over the left ventricle were diphasic or inverted.

A consultation was held by Dr. William H. Higgins, Jr., the patient's personal physician, Dr. Paul D. White, who had referred the patient for study, Dr. A. Stone Freedberg, and Dr. Herrman L. Blumgart. It was agreed that the patient presented no clinical evidence of altered thyroid function. Elevated radioactive iodine uptakes such as those observed in this patient have been described previously in patients who have been on a low iodine diet like the rice diet for considerable periods of time.

In general it was considered that the salient features of this case met the criteria that we have found to be suitable indications for treatment.[1] The patient had continued to have attacks of angina pectoris on the slightest activity during the day and also had attacks at night despite optimal medical management. He had no other disease that made rehabilitation unlikely and he was emotionally stable and cooperative. The clinical course had not been progressively deteriorating. Although the angina pectoris was severe, it had remained at approximately the same levels for some time. Because of these considerations it was decided to recommend radioactive iodine therapy.

Accordingly, 4 doses of radioactive iodine of approximately 10 mc. each were administered at weekly intervals beginning June 20, 1955. In accordance with our general experience, the thyroid uptake of the first therapeutic dose was approximately the same as the tracer dose. Uptakes of the succeeding doses decreased to approximately 20 and 10 per cent. During the patient's stay in the hospital, he continued to have occasional attacks of angina pectoris. On returning home he again had frequent, very severe attacks of angina pectoris requiring meperidine and as many as 50 nitroglycerin tablets daily. The exacerbation of angina pectoris after treatment may have represented spontaneous variation of the condition or may have been due to thyroiditis consequent to the relatively large radiation of the thyroid gland. Even though the administered dosage was small, the estimated radiation delivered by the first dose of 10 mc. was of the order of 30,000 equivalent roentgens, a dose large enough to produce a marked radiation thyroiditis. The patient's personal physician, moreover, noted some thyroid tenderness that suggested thyroiditis.

During the last week of July 1955, 8 weeks after the first dose of I^{131}, the patient noted decided improvement. He was able to walk as much as 250 yards against the wind without anginal pain. On examination in the hospital, the basal metabolic rate was still within normal limits, the cholesterol was 235 mg. per 100 ml., and the protein-bound iodine was 4.4 μg. per 100 ml. An additional dose of 9.3 mc. of I^{131} was administered. The 24-hour uptake was but 9 per cent. During the next month he had only occasional episodes of angina pectoris and showed many clinical and laboratory evidences of hypothyroidism. Accordingly he was started on 1/10 gr. of desiccated thyroid.

Subsequently and up to the present time, the patient has been under supervision of his personal physician and has returned for follow-up studies to us at approximately 6-month intervals. Twenty-one months after I^{131} therapy he continues to be free of attacks of angina pectoris on markedly increased activity, enjoys uninterrupted sleep at night, and has returned to some active participation in his business.

Approximately 6 months after treatment, he experienced paresthesias in his fingers and feet and, although reluctant to take more than 6 mg. of thyroid daily, he was persuaded to increase his dosage to 12 mg. daily. While his basal metabolic rate remained between −20 and −30 per cent, he noted disappearance of the paresthesias without any recurrence of chest pain. When last examined in October 1956, the basal metabolic rate was −30 per cent. The transverse diameter of the heart was the same as that recorded in June 1956, 13.8 cm. The serum cholesterol was 283 mg. per 100 ml. Minimal symptoms of hypothyroidism were present; consequently desiccated thyroid was increased to 18 mg. daily.

Summary. This 66-year-old man with angina pectoris for 17 years before treatment, incapacitated for several years despite long periods of rest and other therapy, showed significant improvement 2 months after I^{131} therapy and for the past 18 months he has been maintained in the hypometabolic state, free of pain despite greatly increased activity.

A PHYSICIAN: The criteria used in the evaluation of the results of treatment in patients with angina pectoris and congestive failure are not clear to me.

DR. BLUMGART: Since both angina pectoris and congestive failure frequently have an irregular clinical course, treatment was administered particularly to the group of patients who had been in a relatively constant state

at least 6 months. For each patient the pretreatment level of disability could be considered as a comparative control for that case. The interval between I^{131} therapy and the onset of hypometabolism, usually several months in duration, constituted an additional control period of observation and minimized the effect of emotional reaction or suggestion to the taking of an "atomic cocktail." Consequently any striking improvement could be confidently attributed to I^{131} treatment.

The evaluation of the effects of treatment has been designated as *excellent*, *worthwhile*, and *not worthwhile*. An excellent result denotes that the patient is markedly improved over pretreatment status, with either no recurrence of symptoms or a marked decrease in the frequency and severity of angina pectoris or congestive failure, despite markedly increased activity; in many instances rehabilitation and return to gainful employment occurred. A good or worthwhile result denotes definite improvement, with a decrease in frequency and severity of attacks of angina pectoris or congestive failure on the same amount of activity as before treatment. The remainder of the patients were thought to have received no worthwhile benefit.

A PHYSICIAN: What have been the results in your patients with angina pectoris?

DR. BLUMGART: Eighty-four of our patients have been followed long enough for evaluation: 36 (43 per cent) had an excellent result, 20 (24 per cent) had a worthwhile result, and 28 (33 per cent) had no benefit. Figure 1 shows these results as well as those previously reported from 49 other clinics. These results also are in accordance with various other published reports.[2-9]

A PHYSICIAN: What objective evidence of improvement has been obtained? Were standardized exercise tolerance tests done?

DR. A. STONE FREEDBERG: Exercise tolerance tests were not carried out in this patient and have not been carried out in similar cases because of the severity of the angina and the possible risks attendant to such tests under these circumstances. Previous studies from this laboratory[10] have demonstrated a marked

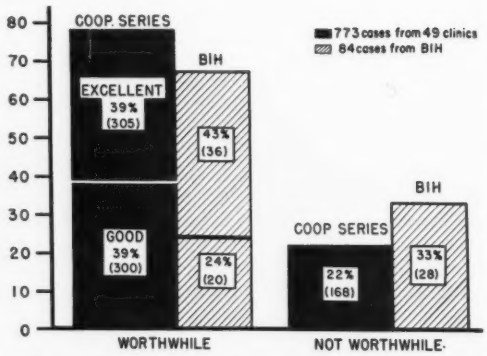


FIG. 1. Results of radioactive iodine treatment of 857 euthyroid patients with angina pectoris in a cooperative series and in a group of cases studied at the Beth Israel Hospital. *Ordinate* indicates percentage of total series.

increase in the standardized exercise tolerance test during induced hypothyroidism.

A PHYSICIAN: Can you attribute the beneficial result to any effect on the blood pressure?

DR. FREEDBERG: No. The blood pressure in our patients is approximately the same after treatment as before. We have observed no changes in blood pressure in any of our patients that might be responsible for improvement in angina pectoris or congestive heart failure.

A PHYSICIAN: Can you anticipate an improvement in life expectancy following the successful treatment with I^{131}?

DR. GEORGE S. KURLAND: An adequate answer to this question must await the collection of extensive data in a large number of patients. Such data must include not only the duration of life after therapy but the duration of angina before I^{131} and the severity of angina. Future studies may answer this point.

A PHYSICIAN: Is there any hazard to I^{131} therapy?

DR. FREEDBERG: With properly controlled dosage there should be no significant hazard to I^{131} therapy. Extensive studies of the blood, urine, and liver function have not revealed toxicity. If the first dose is too large, the excessive thyroid radiation may lead to overt thyroiditis and this has been associated with increased angina. Three instances have been

reported to us of the administration of I^{131} during Dicumarol therapy in which severe hemorrhage into the thyroid gland resulted. We therefore currently regard this combination as hazardous.

A PHYSICIAN: This patient received 5 therapeutic doses of I^{131}. Do all patients receive so many?

DR. FREEDBERG: No. The exact dosage schedule has not been worked out, since no satisfactory method is available to determine in vivo the thyroid radiation delivered by I^{131}. We have estimated that approximately 30,000 to 40,000 equivalent roentgens are required to destroy the normal thyroid gland. The dosage schedule we have evolved is as follows. If the 24-hour uptake of the tracer dose is 30 to 40 per cent, an initial dose of approximately 10 mc. is administered. At the present time, therefore, in a situation such as we had in Mr. W. T., we would administer a smaller initial dose of 7 to 8 mc. If the 24-hour tracer uptake is approximately 20 per cent, we would administer approximately 15 mc. as an initial dose. Correspondingly, with a tracer uptake of approximately 15 per cent, we would administer 20 mc. as an initial dose.

In each instance 2 subsequent doses are administered at weekly intervals, usually 5 mc. larger than the first dose. In recent years we have not administered doses larger than 20 to 25 mc. In an occasional patient additional doses have been administered 6 to 10 weeks later if hypothyroidism has not ensued. Since the thyroid uptake of these doses is very small and the turnover rapid, the doses have been, on the average, 15 to 20 mc.

With this dosage schedule, clinical thyroiditis has been observed only infrequently.

A PHYSICIAN: I notice that this patient was hospitalized. Is that necessary?

DR. KURLAND: The majority of our patients are treated on an ambulatory basis. Only when angina is so advanced that travel to the I^{131} laboratory precipitates severe pain do we advise hospitalization.

A PHYSICIAN: Do diabetic patients in the hypothyroid state have a decreased insulin requirement?

DR. KURLAND: Yes. In several patients who had diabetes and required insulin, hypoglycemic reactions were encountered during hypothyroidism when they continued to take the same dose of insulin. In general, diabetic patients require somewhat less insulin in the hypothyroid state, i.e., approximately 10 or 15 units of insulin less than before.

It has been shown that the glucose tolerance is normal in nondiabetic patients with induced hypothyroidism. Previous studies have shown that the degree of hyperglycemia following glucose ingestion in diabetic patients is less during hypothyroidism.[11]

A PHYSICIAN: What is the effect of the hypothyroid state on heart size in your patients?

DR. KURLAND: We have studied the effect of hypothyroidism on the size and configuration of the cardiac silhouette in 27 patients by comparing roentgenograms taken before and after I^{131} therapy.[12] Ten of 13 patients who achieved good to striking relief of angina pectoris exhibited no increase in the cardiac silhouette after 2 to 48 months of hypometabolism. Two others showed increase in size only during an exacerbation of cardiac pain. On the other hand, 5 of 6 patients not benefited by treatment showed a progressive increase in heart size. In 2 patients with angina pectoris and congestive heart failure, I^{131}-induced myxedema was followed by progressive cardiac enlargement, despite striking therapeutic benefit. The remaining 6 patients with chronic congestive heart failure showed no cardiac enlargement during most of 19 to 53 months of hypometabolism.

We should now like to present a second patient who exemplifies many aspects of the radioactive iodine treatment of intractable congestive failure.

CASE 2

J. K., a 43-year-old woman, had suffered attacks of acute rheumatic fever at 12 and 13 years of age. Although a murmur was recognized after the first episode, she remained well until the occurrence of dyspnea, 6 months before her first Beth Israel hospitalization in October 1951. At this time, she was admitted because of prolonged cough, fatigue, dyspnea, and cyanosis. Examination revealed cardiomegaly, the murmurs of mitral and aortic

stenosis and insufficiency, and rapid atrial fibrillation. There were basal rales and a small pleural effusion. The liver was enlarged but not tender. No evidence of hyperthyroidism, acute rheumatic fever, or bacterial endocarditis was found. When a chest roentgenogram showed previous pulmonary infarction, Dicumarol was administered for 12 days.

After discharge, cardiac decompensation and rapid atrial fibrillation recurred despite vigorous therapy in the cardiac clinic. Five doses of I^{131} totaling 125 mc. were administered from January to August 1952. The 24-hour uptake of the initial dose was 44 per cent. Mild transient thyroiditis occurred. During therapy a second hospital admission was required for severe congestive failure. In August 1952 definite hypothyroidism ensued and the patient noted increased work tolerance without dyspnea or fatigue. The rapid fibrillation was now replaced by slow sinus rhythm. Basal metabolism was −24 per cent; serum cholesterol 263 mg. per 100 ml. Mercurial diuretics, previously necessary weekly or every 2 weeks, were omitted for a while and then resumed only at monthly intervals. A daily dose of 6 mg. of desiccated thyroid was prescribed. She maintained this improvement until October 1954 when, because of a mild increase in dyspnea and ankle edema, mercurials were again administered weekly. Chronic cardiac decompensation was maintained under good control with this regimen until October 1956, when increased frequency of diuretics was required.

Summary. A 43-year-old woman with longstanding rheumatic heart disease and disabling congestive failure despite vigorous therapy was strikingly improved for the first 2 years after I^{131} therapy and moderately improved for the following 2 years.

A Physician: What are the results in congestive failure?

Dr. Blumgart: Thirty-four patients with congestive heart failure have been treated by us: 8 (24 per cent) were strikingly improved, 10 (30 per cent) had a worthwhile result. In 16 (46 per cent) no benefit was obtained. These results and the similar results obtained in 49 other clinics are shown in figure 2.

A Physician: In congestive failure, are the results better in the arteriosclerotic or rheumatic heart disease patient?

Dr. Blumgart: We have been unable to observe any difference in the results in these two groups. We have had striking improvement as well as good and not worthwhile results among both groups of patients.

A Physician: I notice that in the last case sinus rhythm replaced atrial fibrillation after

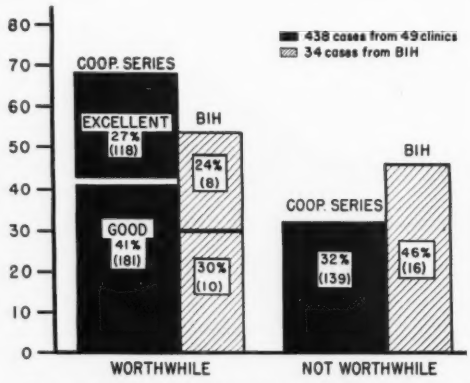


Fig. 2. Results of radioactive iodine treatment of 472 euthyroid patients with congestive failure in a cooperative series and in a group of cases studied at the Beth Israel Hospital. *Ordinate* indicates percentage of total series.

the development of hypothyroidism. Is that common?

Dr. Kurland: In 23 euthyroid patients with rheumatic heart disease and severe congestive heart failure treated with I^{131}, 16 had chronic atrial fibrillation. In 3 of these patients with long-standing atrial fibrillation, the induction of hypothyroidism was accompanied by the spontaneous return of sinus rhythm that then persisted. In no patient did atrial fibrillation develop after the treatment with I^{131}.

Encouraged by these events we have subsequently induced hypothyroidism in 5 patients with uncontrollable paroxysmal supraventricular arrhythmias (3 with atrial fibrillation, 1 with atrial tachycardia, and 1 with both). Four had rheumatic heart disease and 1 hypertensive heart disease. In all, the effect was beneficial. The paroxysms of arrhythmia were abolished or notably diminished in frequency. The bouts that did occur were more readily controlled without precipitation of angina or pulmonary edema.

A Physician: Have you observed the myxedema heart in the sense of a condition precipitating congestive failure in any of your cases?

Dr. Blumgart: As mentioned, certain of our patients showed an increase in the size of the cardiac silhouette, diminished amplitude

of cardiac contraction, lowered voltage of the electrocardiogram, and decreased velocity of blood flow. In no case, however, have we noted evidence of the precipitation of congestive failure in any patient in our series.

A PHYSICIAN: What is the reaction of these patients to other drugs they may be taking, such as digitalis or sedatives?

DR. FREEDBERG: We do not have quantitative data on this question. It is our impression that in some patients less digitalis is required to maintain digitalization. In others, we have been surprised by the continued tolerance to a large maintenance dose. We have also not observed any altered tolerance of these patients to sedatives or, in 6 patients undergoing operation, to meperidine, pentothal, or ether anesthesia. This experience, which is contrary to that in untreated myxedema, may be related to the fact that all our patients receive small doses of thyroid. We do have the impression, however, that similar tolerance to morphine is not present in our patients.

A PHYSICIAN: Have you studied the effects of hypothyroidism on the various lipid fractions?

DR. KURLAND: The serum lipoprotein and cholesterol concentrations have been studied in 15 euthyroid patients with heart disease before I^{131} treatment, during subsequent hypothyroidism, and after administration of desiccated thyroid.

The patients ranged in age from 32 to 82 years; 8 were male; 7 were female. Six suffered from rheumatic heart disease. Two of the rheumatic patients had elevated cholesterol levels before I^{131} treatment. Nine patients had atherosclerotic coronary artery disease with severe angina pectoris. Two or more control serum specimens were generally studied while the patient was euthyroid and from 1 to 6 specimens during the period when the patient was myxedematous.

Additional specimens were obtained after small doses of desiccated thyroid were given to maintain a somewhat higher level, usually −15 per cent to −25 per cent, at which maximum relief of cardiac symptoms and the least possible discomfort from hypometabolism occurred.

Elevation of the most dense lipoprotein fractions, S_f 0–11 and S_f 12–20 correlated better with the presence of hypometabolism than did the less dense fractions above S_f 20. Thus, the initial concentration of S_f 12–20 material ranged from 20 to 72 mg. per cent. Most of these values were within the limits found in normal people of the same age and sex. After the induction of myxedema, the S_f 12–20 values ranged from 27 to 135 mg. per cent and averaged 79 mg. per cent. The data reveal an increase greater than 15 mg. per cent in S_f 12–20 in 9 patients, and none or a small increase, less than 15 mg. per cent, in 6 patients. The 4 patients with rheumatic heart disease and without initially elevated lipids showed a mean initial value of 38 mg. per cent and a value in myxedema of 55 mg. per cent, an average increase of only 17 mg. per cent; however, 3 of these 4 patients showed only minimal increases. Additional studies were obtained in 9 of these 15 patients following the administration of small doses of desiccated thyroid. Two patients showed no change in the concentration of S_f 12–20 or a slight increase. In all the others, there was a downward trend of level that was largest in those cases that had previously shown the greatest increase; in about half the S_f 12–20 level returned to the pretreatment level.

In the S_f 30–35, S_f 35–100, and S_f 100–400 fractions no striking changes were observed.

The serum cholesterol levels showed more marked changes. The initial cholesterol values averaged 223 mg. per 100 ml. in the rheumatic patients; 263 mg. per 100 ml. in the angina patients. In 13 of the 15 patients, the serum cholesterol rose after myxedema and averaged 304 and 359 mg. per 100 ml. for the rheumatic and atherosclerotic patients respectively. With one exception, there was a decline following the administration of thyroid. The serum cholesterol levels correlated better with changes in metabolic state than did the lipoproteins.

A PHYSICIAN: Has any therapy except thyroid been effective in lowering the serum cholesterol in these patients?

DR. KURLAND: We have administered a sus-

pension of sitosterols* to 1 patient with marked hypercholesterolemia associated with I^{131}-induced hypometabolism. The serum cholesterol fell from approximately 700 mg. to 400 mg. per 100 ml. This is similar to the effect observed by Best and Duncan.[13] It is too soon to evaluate the duration or effectiveness of this agent. Experience with other agents such as high unsaturated fat diet, low-fat diets, thyroxin, and triiodothyronine analogues, while promising, is too limited for a definite statement.

In the treatment of congestive failure by radioactive iodine certain other aspects are exemplified by the following case:

Case 3

Patient N. B. was a white man, 35 years old at death. He had had chorea and several attacks of rheumatic fever in childhood.

Physical examination had disclosed cardiac enlargement and the murmurs of aortic and mitral stenosis and insufficiency. He had carried on fairly successfully but finally entered the Beth Israel Hospital in January 1950 at the age of 29 because of increasing exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, occasional precordial aching unrelated to exertion, nonproductive coughing, and rare episodes of dysphagia during the preceding 4 months. Examination disclosed a tall, thin man whose respirations were labored at a rate of 30 per minute; the apical pulse was irregular at a rate of 108 per minute. The initial blood pressure was 160/100 mm.; all subsequent blood pressure determinations were within normal limits. The heart was greatly enlarged. There were loud, rough apical systolic and diastolic murmurs and thrills, softer aortic systolic and diastolic murmurs, a loud pulmonic second sound, and a soft aortic second sound. There was slight cyanosis but no clubbing of the fingers. The neck veins were not distended, the lungs were clear, the liver edge was palpable, and edema was absent. Laboratory studies, including complete blood counts, plasma nonprotein nitrogen, Hinton serologic reaction, and urinalysis were normal except for 2+ to 4+ albuminuria. The arm-to-tongue circulation time was 32 seconds. The vital capacity was 2.1 L. (normal 4.3 L.). Chest fluoroscopy disclosed enlargement of all cardiac chambers, most marked in the left atrium. The lungs appeared slightly congested, and the costophrenic angles contained a small amount of fluid. Electrocardiograms showed atrial fibrillation, right axis deviation (120°), and probable right ventricular hypertrophy. Treatment with rest, low-salt diet, continuation of digitalis, and mercurial diuretic injections every other day resulted in lessening of dyspnea and a 12-pound weight loss, whereupon he was discharged.

Because of gradual relapse on this regimen he was rehospitalized from March to May 1950. Additional studies disclosed a venous pressure of 18.5 cm. of saline and an icterus index of 28 units. Basal metabolic rates averaged +5 per cent, and the 24-hour thyroid uptake of radioiodine was 37 per cent. As a final therapeutic measure, this euthyroid patient was given 32 mc. of radioiodine in 2 divided doses in April 1950.

His condition was unchanged until September 1950, when hypothyroidism appeared. Thereafter, exertional capacity improved considerably, and mercurial injections were required only every 2 weeks. Chest roentgenograms during this period showed slight diminution in cardiac size and clearing of pulmonary congestion. In January 1952, thyroid, 6 to 18 mg. daily, was instituted to alleviate symptoms of myxedema. The basal metabolic rate was maintained at an average of −25 per cent and the serum cholesterol level varied from 280 mg. to 400 mg. per 100 ml. He was able to return to full-time work for the next 4 years.

In August 1955, exertional dyspnea reappeared. In October, the appearance of mild cough, chills, and fever necessitated rehospitalization. The cardiac findings were unchanged. There were now neck vein distention, dullness, decreased breath sounds, and crepitations over the right lower posterior chest, moderate hepatomegaly, and slight leg edema. No evidence of thrombophlebitis was found. The chest roentgenogram showed increased cardiac enlargement and consolidation of the right middle lobe that was interpreted as a possible pulmonary infarct. The electrocardiogram disclosed increased evidence of right ventricular hypertrophy. In conjunction with the cardiac therapy, heparin was administered intravenously every 4 hours, in 50-mg. doses. Dyspnea increased, cyanosis, hypotension, stupor, and periodic breathing developed, and he died on the third hospital day.

Postmortem examination revealed marked stenosis and calcification of the mitral valve, minimal commissural fusion between 2 of the aortic cusps, and slightly thickened and rolled borders of the tricuspid valve with slight thickening and shortening of the chordae tendineae. The pulmonic valve was normal. There was marked dilatation and hypertrophy of the ventricles. The left atrium was huge and contained more than 2 L. of blood; the right atrium contained approximately one third this volume. The coronary arteries examined by the injection and dissection technic of Schlesinger had only a few discrete, nonstenosing atheromatous plaques in the main left and right stems.

The final pathologic diagnoses were moderately active rheumatic heart disease, mitral stenosis and

* Cytellin, supplied through the courtesy of Eli Lilly & Co.

insufficiency, slight commissural fusion of the aortic valve, cardiomegaly, enormous atria with fibrosis and calcification, chronic passive congestion of the lungs, recurrent chronic pneumonitis of the right middle and lower lobes, severe pulmonary atherosclerosis, pulmonary emboli, cardiac cirrhosis of the liver, healed renal infarcts, and thyroid fibrosis and atrophy following radioiodine therapy.

In summary, a 35-year-old draftsman, invalided by rheumatic heart disease and refractory congestive heart failure, was treated with I^{131}. Following development of hypothyroidism, improvement was striking and the patient was able to return to work. He died of a pulmonary complication after 4 years of improvement. Despite hypometabolism for 4 years and hypercholesterolemia of 250 to 400 mg. per 100 ml. for at least 2 of these 4 years, careful study of the coronary arteries revealed no occlusions or major narrowing and only a few nonstenosing plaques.

A PHYSICIAN: To what degree does the increased serum cholesterol level of hypothyroidism cause increased coronary arteriosclerosis in the patient with angina pectoris of atherosclerotic etiology?

DR. FREEDBERG: I presume you are referring to the question whether the high cholesterol values of myxedema dispose the patient to an increased progression of arteriosclerosis. The situation in our patients is not strictly analogous to untreated complete myxedema, since we prescribe or administer small doses of thyroid and we have indicated above the effect that this may have on the serum lipoproteins. We have reviewed the clinical course and postmortem findings of patients who survived from 1 to 11 years after surgical total thyroidectomy and in whom hypometabolism with elevated cholesterol values was present.

We have been particularly interested in the younger patients with rheumatic heart disease. In them only slight or minimal coronary arteriosclerosis would ordinarily be anticipated at death. If decided arteriosclerotic lesions were observed post mortem in such patients, the lesions might well be attributed to the myxedematous state. In a study reported previously,[14] the clinical and postmortem findings are described in 8 such patients with rheumatic heart disease or cor pulmonale, in whom hypothyroidism or myxedema was present and who survived from 1 to 13 years (average, 7.4 years) following surgical total thyroidectomy. None of the 8 cases showed complete occlusion of any of the coronary arteries; 5 of the 8 showed no narrowing of any of the main stems or branches of the coronary arteries; only 3 of the 8 showed slight narrowing of 1 of the main stems. In the other arteries, atheromatosis and atherosclerosis varied greatly, but was similar to that usually observed in similar euthyroid patients.

Our results do not, of course, disprove a role of cholesterol in the production of atherosclerosis; these results do demonstrate, however, that over the observed period of time, the hypothyroid state, controlled with small daily doses of desiccated thyroid, is not necessarily, in itself, sufficient cause for the production of coronary atherosclerosis.

It is of particular interest in patient N. B., case 3, that after hypometabolism was induced by I^{131}, the basal metabolic rate was maintained at a level of approximately −20 per cent for 4 years and the serum cholesterol was significantly elevated as high as 400 mg. per 100 ml. for at least 2 years. When the heart was carefully examined by the technic of Schlesinger, there was no evidence of coronary occlusion or major narrowing of any of the coronary vessels.

A PHYSICIAN: How do you deal with the problem of increasing angina pectoris or congestive failure in your hypothyroid patients when you cannot lower the thyroid medication further without causing intolerable symptoms of myxedema?

DR. BLUMGART: It is fortunately a relatively small group of patients in which one is confronted with this difficult problem. The patient cannot tolerate any further lowering of the metabolic state and has now progressed so that his angina pectoris or congestive failure is similar to that before treatment. Under such circumstances nothing further can be done than the usual methods of treatment; in the instance of angina pectoris, surgical methods of treatment must be considered, including alcohol injections of nerves, ganglionectomy, introduction of foreign substances within the pericardium, or even posterior rhizotomy.

A PHYSICIAN: What do you believe are the mechanisms whereby improvement is achieved?

DR. FREEDBERG: Various considerations lead to the conclusion that the reduction in cardiac work consequent to induced hypometabolism is, in all probabliity, the most important factor. The beneficial effect of rest, and the consequent reduction in cardiac work, in the successful treatment of congestive failure, has long been known. Means[15] in 1924 in discussing the treatment of cardiac dyspnea noted:

> First of all comes treatment directed towards reduction of the metabolic rate. This is seen most strikingly in treatment by rest, particularly in heart failure. Mere confinement to bed, of course, makes total metabolism closely approach basal and, therefore, greatly diminishes the work both of the heart and the respiratory organs and consequently, the dyspnea. . . In the dyspnea of hyperthyroidism . . . those measures which reduce the hyperthyroidism and therefore the metabolism by the same token diminish or abolish dyspnea.

In 1930, it was noted that the velocity of blood flow in patients with myxedema, in the absence of circulatory insufficiency or congestive heart failure, was slower than in normal individuals; in fact, the rates were similar to those observed in patients with congestive heart failure.[16] This led to the concept that reduction of the metabolic demands to a level more closely approaching the blood supply by the institution of hypothyroidism or myxedema might be beneficial to the patient with congestive heart failure. The general validity of this concept has been confirmed by the results obtained following surgical total thyroidectomy, by thiourea derivatives, and, as reported here, by radioactive iodine.

A recent paper by Davies, McKinnon, and Platts[17] suggests another mechanism whereby myxedema may benefit the patient with congestive failure. They observed that patients with myxedema, in contrast to patients with congestive heart failure, had unimpaired ability to excrete salt and water. It was particularly striking that a patient with mitral stenosis and spontaneous myxedema had a glomerular filtration rate and renal blood flow similar to that observed in congestive heart failure, but the administration of a 10-Gm. salt intake and 1,500 ml. of fluid daily did not result in an increase in body weight or a rise in venous pressure, as in patients with congestive failure.

Certain of these considerations are applicable to angina pectoris. It is well established that many patients with angina pectoris and thyrotoxicosis are markedly improved or show a disappearance of angina pectoris when the metabolic rate is reduced to normal. The cost of cardiac work in hyperthyroidism has been shown by Plummer and Boothby[18] to be increased, so that the cardiac work of the thyrotoxic patient at rest is like that of a normal person doing light work. A general reduction in body metabolism in euthyroid individuals with a consequent reduction in requirements for cardiac work would be of obvious importance in improving angina pectoris occurring at rest. It is difficult, however, to relate the small increase in cardiac efficiency and the decreased cost of cardiac work, noted by Briard and co-workers[19] in myxedema to the marked increase in tolerance of exercise noted by patients with angina pectoris in whom hypothyroidism is induced. Moreover, though in most instances clinical improvement in angina pectoris occurs *pari passu* with the drop in metabolic rate, in a few instances clinical improvement is noted early in the period of reduced metabolism and in others only after several months or longer.

Other possibilities suggested as the mechanisms for the improvement that occurs in intractable angina pectoris after induction of controlled hypothyroidism include (1) a decrease in sensitivity of the cardiovascular system to adrenergic mediators, (2) an alteration in pain perception, and (3) an increased rate of development of intercoronary arterial collateral circulation. There is much evidence to indicate an interrelationship between the thyroid hormone, the adrenal cortical hormones, and the catechol amines, epinephrine and norepinephrine. Raab[20] has recently summarized the evidence, "that the thyroid hormone affects the myocardial metabolism by markedly potentiating the hypoxia producing calorigenic and toxic action of the adreno-sympathogenic cortical amines." Since in myxedema there not only is reduction of the thyroid hormone but also in the adrenal cortical hormones, the pos-

sibility cannot be excluded that some local myocardial or coronary vascular change explains the beneficial effect of induced hypothyroidism. Our own data[21] have revealed little change in the systemic pressor response to norepinephrine in euthyroid patients with cardiac failure before and after I^{131}-induced hypothyroidism; Riseman and co-workers[22] also observed little alteration in blood pressure response to epinephrine after surgical total thyroidectomy in patients with angina pectoris until the basal metabolism had fallen to −30 per cent. Of the other possibilities, no evidence exists that the beneficial effect of hypothyroidism is to alter pain perception or to effect a beneficial change in the rate of development of the intercoronary arterial circulation. Much further work is necessary to elucidate these various possibilities.

REFERENCES

[1] Blumgart, H. L., Freedberg, A. S., and Kurland, G. S.: Treatment of incapacitated euthyroid cardiac patients by producing hypothyroidism with radioactive iodine. New England J. Med. **245:** 83, 1951.

[2] Jaffe, H. L.: The multiple small dose radioiodine technic for the treatment of severe cardiac disease in euthyroid patients. Ann. West. Med. & Surg. **5:** 916, 1951.

[3] Stuppy, L. J.: Radioiodine treatment of euthyroid cardiac disease: Introduction. Ann. West. Med. & Surg. **5:** 913, 1951.

[4] Pobirs, F. W.: Clinical course and illustrative cases. Ann. West. Med. & Surg. **5:** 919, 1951.

[5] Wolferth, C. C., Chamberlain, R. H., and Mead, J. J.: Radioactive iodine in the treatment of angina pectoris. Pennsylvania M. J. **54:** 352, 1951.

[6] Rosenfeld, M. H.: Results obtained by treating severe cardiac disease in euthyroid patients with radioiodine. Ann. West. Med. & Surg. **5:** 923, 1951.

[7] Jaffe, H. L., Rosenfeld, M. H., Pobirs, F. W., and Stuppy, L. J.: Radioiodine in treatment of advanced heart disease; end results in one hundred patients. J.A.M.A. **151:** 716, 1953.

[8] Duffy, B. J., Jr.: Radioisotopes in heart disease. M. Ann. District of Columbia **24:** 112, 1955.

[9] Goldman, A. M.: Use of radioactive iodine for intractable angina pectoris. J. Louisiana M. Soc. **108:** 337, 1956.

[10] Blumgart, H. L., Riseman, J. E. F., Davis, D., and Berlin, D. D.: Therapeutic effect of total ablation of normal thyroid on congestive heart failure and angina pectoris. Arch. Int. Med. **52:** 165, 1933.

[11] Gilligan, D., Abrams, M. I., and Stern, B.: Carbohydrate metabolism in human hypothyroidism induced by total thyroidectomy. I. The glucose tolerance curve and the fasting serum sugar concentration. Am. J. M. Sc. **188:** 790, 1934.

[12] Kurland, G. S., Schneckloth, R. E., and Freedberg, A. S.: Heart in I^{131} induced myxedema: Comparison of the roentgenographic and electrocardiographic findings before and after induction of myxedema. New England J. Med. **249:** 215, 1953.

[13] Best, M. M., and Duncan, C. H.: Effects of sitosterol on the cholesterol concentration in serum and liver in hypothyroidism. Circulation **14:** 344, 1956.

[14] Blumgart, H. L., Freedberg, A. S., and Kurland, G. S.: Hypercholesterolemia, myxedema, and atherosclerosis. Am. J. Med. **14:** 665, 1953.

[15] Means, J. H.: Dyspnea. Medicine **3:** 309, 1924.

[16] Blumgart, H. L.: The velocity of blood flow in health and disease. Medicine **10:** 1, 1931.

[17] Davies, C. E., Mackinnon, J., and Platts, M. M.: Renal circulation and cardiac output in "low output" heart failure and in myxedema. Brit. M. J. **2:** 595, 1952.

[18] Plummer, H. S., and Boothby, W. M.: The cost of work in exophthalmic goitre. Am. J. Physiol. **63:** 406, 1923.

[19] Briard, S. P., McClintock, J. J., and Baldridge, C. W.: Cost of work in patients with hypermetabolism due to leukemia and to exophthalmic goitre. Arch. Int. Med. **56:** 30, 1935.

[20] Raab, W.: Myocardial metabolism in the pathogenesis and treatment of angina pectoris. Cardiologia **22:** 291, 1953.

[21] Schneckloth, R. E., Kurland, G. S., and Freedberg, A. S.: Effect of variation in thyroid function on the pressor response to norepinephrine in man. Metabolism. **11:** 546, 1953.

[22] Riseman, J. E. F., Gilligan, D. R., and Blumgart, H. L.: Treatment of congestive heart failure and angina pectoris by total ablation of the normal thyroid gland. XVI. The sensitivity of man to epinephrine injected intravenously before and after total thyroidectomy. Arch. Int. Med. **56:** 38, 1935.

CLINICAL PROGRESS

Diagnostic Value of Translumbar Aortography

By B. J. KOSZEWSKI, M.D., AND W. J. REEDY, M.D.

A historical review of aortography is made that substantiates its present status as a diagnostic tool, particularly in angiology and urology. The technic, premedication, and anesthesia are discussed in detail. The hazards of the procedure and their prevention are reviewed. The reactions to contrast media are enumerated. Aortography plays a selected but important role in the evaluation of aortic aneurysms, arterial occlusion, and stenosis of major vessels. Its value in the diagnosis of abdominal abnormalities is less encouraging. Numerous urologic disorders are discussed in their relationship to angiographic study.

AORTOGRAPHY was introduced in 1929 by Dos Santos,[1, 2] who, inspired by the work of Egas Moniz on cerebral angiography, reported a series of 300 cases in which the abdominal aorta was visualized by translumbar puncture. The diagnostic advantages of the method and its physiologic implications have been conclusively demonstrated. Balestra,[3] Osorio,[4] and others[5, 6] confirmed these findings and stressed the harmlessness of the method. In spite of these favorable statements the procedure did not find its way into clinical practice. The difficulties were probably caused by lack of a proper contrast medium. Early examiners used sodium iodide, which was difficult to handle and proved to be toxic in animal experiments.[7] Thorotrast was an unsatisfactory medium because of severe damage due to its radioactivity and storage in the reticuloendothelial system.[8] The situation improved with the introduction of water-soluble contrast media that diminished the hazards of the procedure and opened the way to new trials. Saito and Kamikawa[9] as well as Castellanos and Pereiras[10] obtained aortograms by countercurrent injection; later, a catheter was introduced high into the aorta.[11, 12] Nelson[13] and Doss[14] revived interest in the translumbar method as they demonstrated that the procedure is reasonably safe, easily performed, and accurate.

Several authors described large series of cases outlining its importance for angiology and urology.[15-25] Complications were very few. Up to the year 1947 Dos Santos[26] performed 3,000 aortographies without an immediate fatality. Smith[22] reported 1,500 consecutive translumbar renal arteriographies without any serious accident.

From the Department of Medicine, Creighton University School of Medicine and Creighton Memorial St. Joseph's Hospital, Omaha, Neb.

TECHNIC

The performance of translumbar aortography generally follows the technic of Smith[22] as described subsequently. The importance of teamwork consisting of operator, roentgenologist, and anesthetist must be stressed. Each member should have adequate knowledge of the anatomy and topography of the area involved in translumbar aortic puncture.

Preparation and Premedication

The patient is prepared with a cleansing enema on the preceding evening and given a laxative to empty the colon. The following day food is withheld until the examination is performed. In the morning 100 mg. of cortisone is given orally to prevent anaphylactic reactions to dye.[28] A quickly acting barbiturate is administered 2 hours before the procedure and meperidine (Demerol) and atropine are given 1 hour preoperatively. When spinal or general anesthesia is used, sedatives may be discarded. Atropine should be used regularly to prevent occasional arterial spasms after the injection of contrast medium.

A test for sensitivity to the contrast media is performed prior to the procedure. The intradermal injection, often recommended in the literature,[27] is impractical, since the highly concentrated media cause skin irritation and sometimes necrosis. A better method is the intradermal test with dye diluted in the patient's serum with readings after 8 and 24 hours.[28] The intraocular route of testing[31] may also be used although irritation of the eye

occurs without any other evidence of hypersensitivity. Intravenous injection of 2 ml. of dye should be performed in the operating room and the patient observed closely for about half an hour.[22] In case of hypersensitivity aortography should be abandoned as the reactions to dye are unpredictable.

Anesthesia

In the early era of aortography general or spinal anesthesia had been used exclusively because the dye injection was very painful.[2] At present this is necessary only when the patient cannot cooperate, i.e., in children, or neurotic, or very senile persons.[31, 32] In these cases intravenous anesthesia with 2.5 per cent sodium pentothal supplemented by gas may be given. However, general anesthesia in the prone position is always dangerous and regularly requires intubation. The dye injection necessitates relatively deep anesthesia followed by a period of nonstimulation, which may lead to longer and deeper postoperative depression.[34]

Local anesthesia can be recommended for routine use.[32] It causes only little distress. The patient can be informed about each step so as to lessen his anxiety and enlist his cooperation.[34]

The patient is placed in the prone position, his back being cleansed and surgically draped. An intradermal procaine wheal is made at a point below the twelfth rib about 10 to 12 cm. to the left of the spinal processes. The subcutaneous tissues and deep muscle layers are infiltrated with a 3-inch, 21-gage needle, which is directed superiorly, ventrally, and medially toward and around the spine. The vertebral body has to be anesthetized carefully to avoid pain. The para-aortic tissues should be infiltrated since "splanchnic anesthesia" markedly diminishes the incidence of untoward reactions during dye injection.[2] Goodwin and Walter[35] injected procaine into the aorta for the same purpose.

The routine use of local anesthesia is not in accord with the opinion of many roentgenologists. Dotter and Steinberg in their comprehensive account of angiography seemed to favor the use of general anesthesia.[36]

Intra-aortic Dye Injection

During or before anesthesia, a scout film of the lower chest, abdomen, and pelvis is made. In this way the position of the spine, the bowel shadows, and the roentgen exposure can be checked. A lead marker at the site selected for skin puncture helps to estimate the direction of the needle and the approximate length of the puncture. It is important to insert the needle rather high in the aorta at the level of the twelfth thoracic vertebra to avoid close contact with the big abdominal vessels. In order to outline the renal arteries some investigators advise insertion of the needle at the level of the first lumbar vertebra to prevent a large portion of the dye passing into the upper abdominal vessels. This procedure is associated with some hazard as the needle enters the "dangerous zone" of Dos Santos[2] near the orifices of the renal and superior mesenteric arteries. Direct forceful injection of contrast medium into 1 of these arteries may lead to severe complications.[15]

If visualization of the lower aorta or arteries of the extremities is desired, puncture at the level of the third lumbar vertebra may be planned. A stronger opacification of the arteries of the lower extremities will be obtained, but it may be difficult to reach the aorta, which at this point is freely movable and more anterior.

A 6-inch, 18-gage needle fitted with a stylet is satisfactory for the purpose of aortography, but the thin-walled, 17-gage needle with the Huber point is more suitable.[24] The large bore of the needle permits rapid injection. The Huber point promotes better dispersion of the dye in the aorta as the jet of fluid leaves the needle at an angle. The needle is directed always superiorly, ventrally, and medially from the chosen point on the skin toward the body of the vertebra. After the bone is encountered, the needle is withdrawn slightly and reinserted more ventrally until it passes around the spine. At this point the stylet is removed and the needle advanced ½ to 1 cm. until a pulsating blood flow indicates puncture of the aortic wall. This moment is easily recognized as a sense of decreased resistance, similar to puncture of the dura during lumbar puncture.[17] Some caution is necessary at this time as the aortic wall may offer increased resistance and undue pressure can cause the needle to pass through the aorta, enter the abdominal cavity, and injure a viscus.[15]

After the aorta has been entered, tubing and syringe previously filled with contrast medium are attached with Luer-Lok connections to the needle. The tubing prevents direct traction or pressure during the injection, which may cause dislocation of the needle and para-aortic deposition of dye. Polyethylene tubing is transparent and inelastic and can be sterilized by immersion in Zephiran hydrochloride solution for 12 hours. Polyvinyl tubing can be sterilized by autoclaving, but becomes stiff and cloudy.[37]

To increase the concentration of the contrast medium some modifications of this standard technic have been proposed. Large 14-gage needles have been used and contrast medium has been injected simultaneously through 2 needles in the aorta.[38] The benefit from these variations, however, is not enough to justify the increased danger of hemorrhage. The rapidity of the injection seems more important than the quantity of the medium.

The injection of 10 to 30 ml. of contrast medium should be performed in 1 to 3 seconds. Several devices have been developed to speed the injection, but renal complications are more likely to occur with mechanical injectors. Wagner and associates[15]

recommended that the injection be done by hand, so that changes in resistance can be detected. However, the concentration of dye with hand injection may be poor and several other "physiologic" mechanical devices have been proposed.[39, 40]

We use a simple wooden stand that holds a 20 and a 50-ml. Luer-Lok syringe in a stable vertical position. Sufficient force may be exerted on the syringe barrel to deliver the dye within a few seconds.[41] If the injection is started when the aortic blood reaches the syringe, one can feel sure that the needle is in the aorta and air injection is excluded. The syringe should be flushed with warm saline to promote easy motion of the barrel during injection and dye solution should be warmed to body temperature before use to prevent formation of crystals.

The application of elastic tourniquets around the thighs recommended by Dos Santos[1] does not improve concentration of dye in the intraabdominal sector.[18] However, application of blood pressure cuffs inflated above the systolic pressure seems to improve the filling of the renal arteries and the outline of the kidneys.[34] The head-down position, recommended by Dos Santos[2] and Maluf and McCoy[25] is not useful. Pneumoretroperitoneography aids the outline of the organs and their blood supply and may be justifiable in selected cases when retroperitoneal changes are expected.[24] The combination of aortogram with simultaneous retrograde pyelogram is superfluous.[42]

Contrast Media

Dos Santos and his followers used almost exclusively 80 to 100 per cent solution of sodium iodide for radiographic purposes.[2] This medium gives excellent contrast, but produces many untoward reactions. It has a high viscosity and causes painful sensations in the abdomen and extremities. Organic radiopaque dyes have superseded its use, since they give equally good roentgen contrast and few reactions.[16] Organic iodine compounds such as 75 per cent sodium iodomethamate, 70 per cent iodopyracet, and 70 per cent sodium acetrizoate are now used routinely.

Radiography

X-ray technic plays an extremely important role in aortography. The degree of radiopacity differs with the size of the patient, the level of injection, and the expected pathology. For anteroposterior views 25–30 milliamperes at 85–90 kilovolts, and an exposure of $\frac{1}{10}$ of a second are sufficient as a rule.[42] The film should be exposed during injection of the last few centimeters of the dye. The timing is important as the dye is propelled quickly and the maximal concentration may be easily missed. A syringe wired for automatic x-ray exposure was proposed for this purpose.[43] For visualization of the aorta and its branches, a single film is sufficient. This may be accomplished on an ordinary radiographic table with a Potter-Bucky diaphragm and a 36-inch target-film distance. A long cassette, 14 by 34 inches, in conjunction with a long stationary grid may be used to visualize the abdominal aorta simultaneously with the arteries of the legs.[44] Dos Santos[1] recommended stereoscopic films, since superimposition of aortic branches often makes identification difficult. The pictures can be taken simultaneously with a special device, or 2 injections with different position of the tube may be used.

For visualization of the abdominal organs and especially the renal parenchymal vessels, multiple film exposure is necessary. The flow of the dye is better followed and details are visualized that otherwise escape observation. Dos Santos[26] early recognized the necessity of multiple exposures during the course of the injection and others used the method routinely.[21, 45] It was found that the aorta remains outlined for 3 to 4 seconds after the injection. Usually 1 film gives a better picture than the others, depending on the force of the injection. Visualization of the peripheral branches is variable and may precede or follow the optimum filling of the aorta. At least 8 pictures, should be taken, 4 of them at 2-second intervals and the rest 1 to 4 minutes after the injection. The exposure is $\frac{1}{15}$ second with 200 milliamperes at 90–95 kilovolts. In this way the aorta and its main branches will be visualized and the opacification of the abdominal organs, or the pooling of dye in some abnormal structures seen.

In the presence of renal pathology additional films should be exposed 5, 15, and 30 minutes after dye injection. Excretion of contrast substance in the kidney with filling of renal pelvis, ureters, and bladder will be demonstrated.[25]

After-Care

After the dye has been injected, the needle is instantly removed and a sterile dressing applied. An infusion of saline or liberal oral intake of fluid will aid excretion of the dye. When general anesthesia is used, the usual precautions are taken until recovery from anesthesia. In patients examined under local anesthesia the blood pressure and pulse are taken every 30 minutes, but they may be elevated after 4 hours. Medication for pain will be necessary only in cases of extravasation of dye or inadvertent direct injection into renal or mesenteric arteries.

Results

The primary objective of aortography is the demonstration of the aorta and its branches. The degree of vascularity allows conclusions relative to the condition of the abdominal and pelvic organs, especially the kidneys. The artery will be larger than normal with hypertrophy or acute inflammatory lesion of an

involved organ. A decrease in the caliber indicates fibrosis and atrophy of the organ.[23]

Abnormalities of the Aorta and its Branches

Congenital Anomalies. Aortography presents an excellent tool for diagnosis of congenital vascular lesions such as aberrant vessels, arteriovenous fistulas, and aneurysms. Aberrant vessels of the aorta are seldom of clinical significance, but near the kidney they can lead to hydronephrosis through obstruction of the ureteropelvic junction.[14] Congenital coarctation of the abdominal aorta is extremely rare; only 16 cases have been recorded in the last 100 years.[16] In some cases it may lead to heart failure and can be corrected surgically.[46]

Arteriovenous fistulas are usually diagnosed clinically. However, in congenital abnormalities arteriography is necessary to delineate the vessels involved and the size and number of communications.[16] Visualization of post-traumatic fistulas will also be of considerable help in repair.

Congenital aneurysms of the abdominal aorta are extremely rare. Their detection is hampered by the difficulty of aortography in childhood.[31] Several instances of aneurysm of hepatic, splenic, celiac, and renal arteries have been described.[47, 48] They usually contain calcium and can be recognized without aortography except for cases with uncertain localization.[15] These aneurysms are of clinical interest, as they may rupture. Now they can be resected without sacrificing the organ involved.[48]

Aortic Aneurysm. The loss of elasticity in a circumscribed area leads to the formation of an aneurysm. Abdominal aortic aneurysms occur mostly below the level of the renal arteries and are usually arteriosclerotic in origin. They may be recognized clinically as expansively pulsating masses in the abdomen. Sometimes it is impossible to differentiate between the pulsation due to aneurysm and that due to a tumor over the aorta. In the absence of typical roentgenologic signs such as calcification or bone erosion, aortography should be done.[49]

Recognition of aortic aneurysm has become more important, since the condition can be surgically repaired.[50] Aortography will facilitate selection, since extreme dilatation of the aorta and multiple aneurysms are not suitable for surgery. Operative correction is urgent if there is pain because the untreated cases do not survive longer than 3 years.[51]

In rupture of an abdominal aneurysm the life expectancy is extremely short. With aortography it may be possible to demonstrate the condition before death. In a few instances surgical repair may be accomplished.[50]

Atherosclerosis. According to statistical observations the abdominal aorta is most frequently and extensively involved in generalized arteriosclerosis.[23] The changes can be recognized by aortic dilatation and tortuosity. The major branches are large and often show calcifications. Their course is irregularly tortuous because of elongation and loss of elasticity. A decrease in caliber indicates secondary changes in the wall due to fibrosis or thrombosis.[52]

Arteriosclerotic constriction is usually caused by encroachment of an arteriosclerotic plaque and may culminate in obstructive thrombosis or rupture. With an arteriogram the obstructed area and the collateral circulation may be seen. Sometimes even the length of the obstructed segment may be estimated if the distal artery is filled through collateral vessels.[44]

In cases of peripheral arterial disease translumbar arteriography is preferable as the aorta is easily accessible and the damaged femoral vessels are not further traumatized. The danger of arteriospasm is lessened and the collateral vessels may be better visualized. Aortography is imperative when the femoral pulses are absent, as the block must be located in the iliac arteries or higher. Stenosis of the major arteries is more frequent than previously suspected and may simulate the symptoms of peripheral arterial obstruction.[38]

Arterial stenosis or thrombosis may appear in young people and differentiation from arteritis and especially from thrombangiitis obliterans is often necessary. In arteriosclerosis the arteries are wide and show an irregular course and contour. In arteritis the narrowing of the lumen is concentric and the vessels are small. They always have a curved course without angulation.[18]

Aortography is just as helpful in cases of embolism as it is in the diagnosis of arterial

thrombosis. It gives the exact position of the embolus.[53]

Leriche's Syndrome. Thrombosis of the bifurcation of the abdominal aorta was recognized by Leriche[54] as a distinct clinical pathologic entity. It manifests itself gradually and is characterized by fatigue in the legs, intermittent hip claudication, loss of firm erection, absent femoral pulses, symmetrical moderate atrophy of the legs, and signs of impaired circulation without trophic changes of the skin or toenails. The obliteration usually originates in 1 of the common iliac arteries, but the thrombus soon extends proximally, reaching the terminal aorta. The aorta may be blocked completely or partially. The thrombosis may spread upward toward the origin of the mesenteric and renal arteries. The condition is more frequent than is generally realized, the autopsy incidence being 0.1 per cent.[55] Aortography is of great value in diagnosis and is evaluating the extent of involvement and of the collateral circulation. With the block at the aortic bifurcation, enlarged intercostal and lumbar arteries and anastomoses of the inferior mesenteric artery with branches of the hypogastric arteries may be seen. If the thrombosis reaches the inferior mesenteric artery, the collateral vessels between the middle and left colic artery dilate. If the block is higher, the collateral circulation will be between the internal mammary and inferior epigastric arteries.[18]

Progressive thrombosis of the lower abdominal aorta may be compensated for many years by collateral circulation. Sooner or later it leads to grave ischemic phenomena in the lower extremities due to secondary peripheral changes. Death usually occurs from gangrene and infection of the extremities, or from coronary heart disease. In cases with thrombosis of the renal arteries, hypertension and renal insufficiency are the outcome.[41]

Early recognition of aortic thrombosis is very important, since resection of the aortic bifurcation is technically possible and the circulation to the extremities may be restored with a homologous graft or synthetic prosthesis.[56]

Chronic thrombotic occlusion should be differentiated from acute embolism involving the aortic bifurcation. In the latter case the onset is always acute and associated with severe shock and violent pain. Because of inadequate collateral circulation, paraplegia and ascending gangrene are likely. Translumbar aortography will outline the so-called saddle embolus and facilitate embolectomy.[53]

Diagnosis of Abdominal Abnormalities

Disease of the abdominal organs may be recognized from the status of the arteries supplying them.[27] Abnormal dilatation, stenosis, or obstruction of an artery indicates pathologic change. The course of the arteries from the celiac axis may give information about the liver, spleen, and the mesenteric arteries. Physiologic variations are so numerous, and our experience so meager, however, that exact diagnosis is often difficult.

In aortic seriography the abdominal diagnosis is facilitated by the outline of the spleen and liver, due to retention of the dye in the sinusoids. Parenchymal opacification is very pronounced in the kidney and the spleen, and distinctly less in the liver.[57]

Splenic enlargement, rupture of the spleen, and accessory spleens may be diagnosed by means of the splenogram.[18] Epigastric tumors may be visualized if they are large enough to dislocate vessels. However, undoubtedly positive results are rare. Enlargement of the liver may be substantiated by the hepatogram.

Primary or secondary tumors of the liver may be seen if they displace branches of the hepatic artery or if they cause defects in the homogeneous hepatic opacification.[58] Advanced cirrhosis of the liver gives only a faint contour. The association of cirrhotic liver with enlarged mesenteric vessels observed by Nelson[13] has not been substantiated in subsequent series.[34]

Disease of the mesentery and intestine can be inferred from angiograms of the superior and inferior mesenteric arteries. The displacement of major arteries and filling defects in some parts of the ansiform loops permit recognition of tumors of the mesentery. However, the mesenteric angiogram is difficult to interpret as the ansiform loops overlap frequently. Sometimes pooling of contrast medium in abnormal vessels of a malignant tumor makes the diag

nosis possible.[24] The positive results are too rare to warrant using translumbar aortography as a diagnostic tool in recognition of intestinal tumors.

Exploration of the upper retroperitoneum with aortography is rather disappointing. The filling of hepatic and splenic arteries and the resulting splenograms and hepatograms obscure the details in this part of the abdomen and limit the conclusions that can be drawn. Several attempts to visualize pancreatic tumors failed in our series.[34] Attempts to demonstrate the site of bleeding in upper gastrointestinal hemorrhage with aortography proved futile.[59] Tumors of the adrenal glands may be recognized by observation of the size and distribution of the suprarenal arteries or by displacement of adjacent blood vessels.[60] Adrenal carcinoma may also cause downward displacement and flattening of the kidney. In some cases pooling of contrast medium in a suprarenal tumor may be seen.[13] Aortography is decidedly inferior to retroperitoneal air insufflation, which renders good outlines of the kidney and glands.[61]

Masses in the lower retroperitoneum have been diagnosed by displacement of the aorta and kidneys.[41] Abnormalities of the lumen and pressure defects are rare due to the elasticity of the aortic wall, but the abdominal aorta is movable and readily gives way to external pressure. Deformation and displacement of the renal shadow may be of diagnostic aid.

Demonstration of pelvic disease by means of aortography is seldom indicated because the diagnosis can be made by simpler methods. The conclusions concerning the course of the hypogastric arteries and branches are invalid, since these vessels show many physiologic variations that cannot be differentiated from pathologic changes. Only tumors with increased vascularity will be clearly demonstrated.[6] In cases of large uterine myoma "a hairpin bend" of the uterine artery and an increase in its width were reported.[62]

Differentiation between ovarian tumors and growths arising from the uterine wall by means of a different blood supply, has not been satisfactory.[62, 63] When a fibroma is associated with an ovarian tumor, the correct diagnosis is impossible.

The maternal circulation of the placenta has been studied by means of translumbar aortography.[6] The blood sinuses give a characteristic mottling in the x-rays and allow determination of the point of attachment. Hartnett[62] was able to establish the correct diagnosis of placenta previa in 2 cases. The method may be of diagnostic value in establishing extrauterine gravidity but its use is limited, since aortography may induce labor in women near term.

In summation it can be said that the use of aortography for abdominal diagnosis is limited. With the exception of tumors in the lower retroperitoneum, the aortogram fails to add additional information to the physical examination, routine x-ray studies, or retroperitoneal pneumography.

Aortography in Urologic Diseases

In contrast to the rather disappointing results of aortography in general abdominal pathology, experiences in the diseases of the kidney are encouraging. Rapid cassette devices opened an entirely new field in urologic investigation.[21] Information includes the status of renal arteries, the condition of the kidney parenchyma, and its excretory function.

Visualization of the renal vessels is of value in demonstrating aneurysms, arteriovenous fistulas, and vascular obstruction due to embolism and thrombosis.[64] Accessory renal arteries from the left side of the aorta, from the proximal portion of the renal artery, and from neighboring vessels will be noted.[64] They usually do not enter the hilus, but pierce the outer surface of the kidney.

The diagnosis of renal abnormalities is aided by the characteristic opacification of the parenchyma with the dye. The phenomenon of nephrography was observed by Hellmer[65] in ordinary pyelography after he used highly concentrated contrast media intravenously. In abdominal aortography, it occurs regularly and helps to analyze the size and the form of the kidney. The opacification of both kidneys occurs usually within 2 to 5 seconds after the major renal vessels are visualized. It is caused by a large concentration of dye within the parenchymal vessels and also by the increased

dye secretion into the tubules. Great density signifies good function and lack of kidney visualization indicates severe renal damage.[14, 34]

Coincident with the nephrogram opacification of the renal vein may be observed. The phenomenon occurs infrequently and its diagnostic implications are still uncertain.

X-rays taken 5 to 30 minutes after the dye injection show an excretory urogram that is helpful in diagnosis of diseases of the pelvis, ureters, and bladder.[25] The pyelogram may be seen even if no significant nephrogram is present. This phenomenon speaks for endogenous kidney disease and has been noted in malignant hypertension, chronic glomerulonephritis, and terminal stages of pyelonephritis.[21] The failure of a pyelogram, together with an absent nephrogram, indicates that the kidneys are nonfunctioning and the pathologic changes irreversible.[34]

Developmental Anomalies of the Kidney. Aortography is of particular value in those cases of renal pathology in which intravenous and retrograde pyelograms do not show the kidney. Agenesis of the kidney can be recognized easily because no renal arteries and no nephrogram is seen.[42] In hypoplasia of the kidney the artery is small and has only a few branches; the nephrogram shows a small and faintly outlined kidney.[66] The pelvis and ureter are small in the resulting urogram. Horse-shoe kidney and ectopic kidney are easily detected by means of a nephrogram. In these cases as well as in crossed renal ectopia there are a number of anomalous vessels. In duplication of the kidney 2 separate vascular networks and double pelvis are seen.[56]

Polycystic Kidney. The main value of aortography in polycystic kidney is the determination of potential renal function with resulting information about the prognosis. Failure to visualize the kidney in serial examination is a sign of renal insufficiency and bad prognosis.[21]

Differentiation between Renal Cyst and Tumor. The differential diagnosis between benign solitary cysts and malignant kidney tumors has always been a difficult problem in urology, as both may produce identical deformity of the pelvicalyceal system. In the nephrogram a solitary cyst appears as a relatively avascular structure with widely divergent large vessels in the periphery.[17] The excretory urogram will reveal transformation of the pelvis according to the size and position of the cyst. The picture may demonstrate not only large cysts near the hilus, but small cysts near the periphery of the kidney.[15]

In contrast to these findings, hypernephroma, if not necrotic shows an increased opacification characterized by "puddling of the dye," due to retardation of blood flow in the highly vascularized tumor.[13, 14] Even a small tumor may be detected if enough medium is retained in the newly formed sinusoidal vessels.[2] Only positive results are conclusive as malignant renal tumors are often associated with necrosis and may contain poorly vascularized zones.[64]

Metastatic cancer may also be seen in nephrograms,[21] but the diagnosis can often be missed. Papillary adenocarcinoma and squamous-cell carcinoma of the renal pelvis will show displacement of the vessels and an abnormal pyelogram may help to identify them.[25]

Hydronephrosis. The etiology of hydronephrosis can be clarified by routine urologic examination. Aortography will be necessary when intravenous pyelography gives poor visualization of the affected kidney and the retrograde pyelogram is unsuccessful. It is also indicated in cases where urinary infection makes retrograde pyelography undesirable. It will help to localize the course and number of the anomalous vessels and to determine how much they contribute to the circulation of the kidney.[14] The function of the kidney may be also ascertained. When the parenchymal changes have advanced so far that they interfere with the blood supply, the kidney should be removed, since it probably will never regain its function.[18] If the vascularity of the kidney is good and a nephrographic effect is obtained, every effort should be made to save the kidney even though the renal cortex is markedly thin.[21]

Chronic Kidney Infections. Aortography is seldom necessary in bladder disease, renal calculi, calculous or tuberculous pyonephrosis and pyelonephritis but it may be useful from the functional aspect, since a good nephrogram

proves good excretory function and indicates good prognosis.

Chronic infection causes a decreased arterial supply to the renal parenchyma and a poor nephrogram.[52] The vessels are spread apart and decreased in number. They may be stretched, displaced, or bent and often show abrupt terminations. The differentiation between actually decreased circulation and incomplete filling is not easy and can be accomplished only by routine use of a rapid cassette changer permitting adequate study of the aorta, the renal arteries, and their terminal branches.[34]

Recently aortography has gained attention in connection with tuberculosis of the kidney. The necrotic areas of the renal parenchyma show decreased vascularity and more or less circumscribed dark areas in the contrast-laden kidney. Changes in the renal pelvis may be recognized in later studies. Weyde[21] believed that local or segmental resection of the kidney may be possible if the extent of the lesion and its relationship to the pelvis is known.

Hypertension. The visualization of the kidney vessels is of great value in clarification of some cases of hypertension. Since the experimental work of Goldblatt,[67] it is known that occlusive lesions of 1 or both renal arteries may be related to sustained hypertension. The proof in the majority of cases exists on circumstantial evidence with verification only after death.[68] Recently such cases have been recognized by means of aortography.[41] The procedure should be contemplated in patients with an acute onset of hypertension that is associated with an episode of abdominal pain or trauma.[66] It will demonstrate the unilaterality or bilaterality of the disease, the changes in the caliber and the walls of the renal arteries, and the degree of renal ischemia.

In renal infarction an abrupt termination of arterial branches is seen with an avascular distal segment of parenchyma.[52] In older infarctions a depression of the renal cortex may be perceived in the seriogram. Multiple renal infarctions may lead to hypertension as the zone of diminished viability around the necrotic tissue may liberate substances of hypertenzinogen-like action.[68]

Hypertension may also be the result of unilateral kidney disease that causes atrophy of the parenchyma and vessels. The recognition of these cases is extremely important as operation can eliminate the pathogenic mechanism and relieve the hypertension.[67]

In selected cases of essential hypertension aortography may give prognostic clues through the study of arterial supply and the degree of kidney opacification.[66] An absent nephrogram indicates a poor prognosis, especially if the hypertension is of short duration.

Contraindications and Complications of Aortography

For many years translumbar aortography was regarded as a difficult and dangerous procedure and the indications for its use were ill defined. These same obstacles embarrassed pyelography in its early stages before frequent use over many years established it as an essential diagnostic tool.

A distinct warning against the method was issued by Henline and Moore[7] following an experimental study of 19 dogs in which the aorta was punctured through the posterior approach. Five animals died from traumatic hemorrhage shortly after the aortic injection, and 3 apparently from toxicity of sodium iodide. Dos Santos[26] pointed out repeatedly that the risk of hematomas in dogs is greater than in human beings. Extravasation of blood does occur in human beings but the valvular effect of the oblique passage ensures rapid closure following withdrawal of the needle.[2] Inadequate anesthesia during injection may permit movement of the patient and lead to a tear in the aorta and extravasation of the dye. Hemorrhage is probably responsible for the occasional lower left chest pain and left shoulder pain. Injection of the medium intramurally or outside of the aortic wall results in a painful sensation in the back or in the epigastrium, but the expected tissue necrosis and damage to the aortic wall have proved to be rare.[16] Deterling[69] described a severe and prolonged chemical neuritis of the lumbar nerves.

Because of possible rupture, aneurysm or extensive calcification of a normal-sized aorta has been considered a contraindication to

aortography, but growing experience has not substantiated increased danger of bleeding in these cases.[19]

In their anatomic studies Wagner and co-worker[15] pointed out that injury to neighboring viscera by the advancing needle is most unlikely. Wagner and Price[70] reported entrance of the needle into the azygos system of veins. Maluf and McCoy[25] observed complete severance of the thoracic lymph duct at the level of the tenth to eleventh thoracic vertebrae with resulting chylothorax. A few instances of pleurisy as well as of pneumothorax have been observed.[33] Perforations of an intraperitoneal hollow viscus may also occur.[16] Shapiro[23] described injury of the splenic artery that necessitated splenectomy.

Wagner and Price[70] reported a fatality from mesenteric thrombosis with gangrene of the intestine. The needle was inserted into the orifice of the superior mesenteric artery and the entire amount of 80 per cent sodium iodide injected into its branches. There was no autopsy in this case. Melick and Vitt[16] observed a similar event with death in 48 hours due to gangrene of the bowel, but the autopsy revealed generalized intestinal carcinomatosis. Several instances of injections into the splenic, hepatic, and renal arteries have been reported in the literature with only minor reactions.[33]

Systemic reactions to dye may occur immediately as hypersensitivity reactions, or may be delayed due to toxic effects upon the parenchymatous organs, particularly the liver and kidneys. Toxic and allergic reactions consist of nausea, vomiting, transient cyanosis or dyspnea, fall in blood pressure, feeling of heat, and sudden death. Premedication does not prevent these symptoms. Drugs do not seem to help in relieving them. However, our recent experience indicates that premedication with cortisone successfully diminishes the frequency and the intensity of these reactions.[28]

Cournand and co-workers[71] found 26 sudden deaths in a group of 6,224 patients who had angiocardiographic examinations. The type of death was usually ascribed to respiratory arrest, during or immediately following injection. To our knowledge only 1 instance of sudden death due to anaphylactic shock following translumbar aortography has so far been reported.[28] The cardiac arrest was preceded by severe dyspnea and urticaria. Facilities for immediate administration of oxygen, epinephrine, and cardiac resuscitation should be available during aortography.

The sensitivity reactions may be prevented by previous testing and careful selection of the patients, although Cournand[71] stated that they cannot be predicted on the basis of skin or eye tests. According to Leriche,[18] aortography is contraindicated in obese persons, and in patients with diminished cardiac output, or impending gangrene of the legs. In these cases the reflex action of the contrast medium with resulting spasm and its direct toxic action on endothelium may lead to arterial thrombosis with fatal results. The iodine-containing dyes should not be used in the presence of severe liver damage, poor renal function, hyperthyroidism, exudative or allergic diatheses, advanced tuberculosis, and sensitivity to iodides. Aortography is strictly contraindicated in patients with renal failure. A blood urea nitrogen of 40 mg. per cent is the limit above which dye injection is not permissible.[42]

Baccaglini and Ballarin[73] found hemorrhages in the glomeruli of the kidney and also in the liver and spleen in dogs. Larsson and Palmlov[19] demonstrated in 38 patients that there is ordinarily no detectable change in the renal function after aortography. A temporary diminution of function occurred only after direct injection of iodopyracet (Diodrast) into the renal arteries. Miller and co-workers[74] reported 7 instances of renal damage following aortography. These complications would probably not occur if no more than 40 ml. of dye were injected.[75] A case of acute renal failure leading to death was reported by Fry,[76] who used an extremely high dose of 100 ml. of 70 per cent sodium acetrizoate (Urokon) in 1 examination.

A grave complication of aortography is paraplegia, which has been reported so far 5 times.[77-80] The pathogenesis of this phenomenon is not clear. Shunts that divert the contrast material into the spinal cord circulation may be responsible for this complication.[79] Evans[42] blamed it on improper technic with the needle passing through the intervertebral disk and spinal canal, thus enabling the dye to escape into the subarachnoid space. The neurologic

symptoms seem to occur in cases where the puncture was performed in the lower lumbar area.

Fortunately the complications of aortography are rare. Most reactions occurred because of improper technic with insertion of the needle below the level of the twelfth thoracic vertebra and injection of dye into 1 of the major branches of the aorta.

Discussion

More than 25 years have elapsed since Dos Santos[1] described the method of translumbar aortography. The accumulated experience indicates that the procedure has brought a high degree of diagnostic efficiency into clinical diagnosis. The examination is relatively simple, since it can be carried out under local anesthesia. It is relatively safe with water-soluble, organic contrast media.

Aortography is a valuable method for examination of the abdominal aorta. Many important diseases that were formerly seen only at autopsy may now be visualized. Proper interpretation depends upon knowledge of the normal aortic tree and familiarity with its variations. Congenital anomalies, arteriovenous fistulas, aneurysms, arterial thrombosis, and emboli may be recognized and treated. The examination is not a routine procedure in patients with peripheral vascular disease, but it may be of immeasurable help in estimation of the extent of the lesion and its correction.

Conclusions concerning pathologic conditions of the abdominal organs can be reached from the status of the arteries supplying them. However, the use of aortography for abdominal diagnosis is limited, as physiologic variations are wide. The aortogram may delineate tumors in the lower retroperitoneum, but it fails to give additional information about the tumors in the upper retroperitoneal space.

Technically successful aortography may reveal valuable information in complicated urologic cases, in addition to what can be demonstrated by cystoscopy and pyelography. It is actually simpler than a retrograde pyelogram and is accompanied by no more reaction Its accuracy has been markedly enhanced since serial exposures were introduced. Valuable information concerning the amount of blood supply to the kidney and its distribution may be obtained. The condition of the renal parenchyma and its excretory function can be studied. Aortography is most useful in cases where no contrast is seen during intravenous pyelography, where retrograde pyelography is unsuccessful or shows only a slight hydronephrosis, and in cases of questionable deformity of the pelvis. It can supply preoperative information about the nonfunctioning kidney. It can visualize anomalous renal arteries and help detect congenital anomalies. Often it will permit the differentiation between renal neoplasm and a solitary cyst.

In selected cases aortography offers information that cannot be obtained by any other method. This is especially true in the field of angiology and urology.

Summary

The diagnostic value of translumbar aortography is discussed. The technic of the procedure is emphasized. Water-soluble, organic iodine media make it reasonably safe. Serial x-ray exposures during dye injection enhance its diagnostic accuracy.

The most valuable information is obtained in the fields of angiology and urology. Some diagnostic help may be gained by the examination of the lower part of the retroperitoneal area.

Summario in Interlingua

Le valor diagnostic de aortographia translumbar es discutite. Le technica del methodo es sublineate. Medios a iodo organic que es solubile in aqua rendo lo satis secur. Roentgenogrammas serial facite durante le injection del colorante augmenta su accuratia diagnostic.

Le plus significative informationes es obtenite in le campos angiologic e urologic. Datos de alicun valor diagnostic pote esser obtenite per examinar le parte inferior del area retroperitoneal.

REFERENCES

[1] Dos Santos, R., Lamas, A., and Caldos, J. P.: L'arteriographie des membres de l'aorte et ses branches abdominales. Bull. mém. Soc. nat. chir. **55:** 587, 1929.

[2] —, —, and —: Arteriographie des membres et de l'aorte abdominale. Paris, Masson et Cie. 1931.

[3] Balestra, G.: L'esploratione radiologica dell' aorta abdominale. Minerva med. **23:** 276, 1932.

[4] Osorio, P. A.: Abdominal aortography. J.A.M.A. **100:** 1955, 1933.

[5] Compan, V.: L'aortographie en service de l'urologie. Arch. Malad. Reins. **9:** 453, 1935.

[6] Coutts, W. E., Opazo, L., Bianchi, T. B., and Denose, O. S.: Abdominal circulation during late pregnancy as shown in aortograms. Am. J. Obst. & Gynec. **29:** 566, 1935.

[7] Henline, R. B., and Moore, S. W.: Renal arteriography; preliminary report of experimental study. Am. J. Surg. **32:** 222, 1936.

[8] Thorotrast: Report of council on pharmacy and chemistry. J.A.M.A. **99:** 2183, 1932.

[9] Saito, M., and Kamikawa, K.: A new modification for the injection method of arteriography (injection in refluence). Am. J. Surg. **17:** 16, 1932.

[10] Castellanos, A., and Pereiras, R.: Countercurrent aortography. Rev. Cubana cardiol. **2:** 187, 1940.

[11] Farinas, P. L.: New technique for the arteriographic examination of the abdominal aorta and its branches. Am. J. Roentgenol. **46:** 641, 1941.

[12] Peirce, E. C.: Percutaneous femoral artery catheterization in man with special reference to aortography. Surg., Gynec. & Obst. **93:** 56, 1951.

[13] Nelson, O. A.: Arteriography of abdominal organs by aortic injection. Surg., Gynec. & Obst. **74:** 655, 1942.

[14] Doss, A. K., Thomas, H. D., and Bond, T. B.: Renal arteriography, its clinical value. Texas State J. Med. **38:** 277, 1942.

[15] Wagner, F. B., Jr., Price, A. H., and Swenson, P. C.: Abdominal arteriography; technique and diagnostic application. Am. J. Roentgenol. **58:** 591, 1947.

[16] Melick, W. F., and Vitt, A. E.: Present status of aortography. J. Urol. **60:** 321, 1948.

[17] Sante, L. R.: Evaluation of aortography in abdominal diagnosis. Radiology **56:** 183, 1951.

[18] Leriche, R., Beaconsfield, P., and Boely, C.: Aortography; its interpretation and value: A report. 200 cases. Surg., Gynec. & Obst. **94:** 83, 1952.

[19] Larsson, H., and Palmlov, A.: Abdominal aortography with special reference to its complications. Acta radiol. **38:** 111, 1952.

[20] Denstad, T.: Abdominal aortography. Acta radiol. **38:** 187, 1952.

[21] Weyde, R.: Abdominal aortography in renal diseases. Brit. J. Radiol. **25:** 353, 1952.

[22] Smith, P. G., Rush, T. W., and Evans, A. T.: The technique of translumbar arteriography. J.A.M.A. **148:** 255, 1952.

[23] Shapiro, D.: Abdominal arteriography. Radiology **60:** 1, 1953.

[24] Walter, R. C., and Goodwin, W. E.: Aortography and retroperitoneal oxygen in urologic diagnosis: A comparison of translumbar and percutaneous femoral methods of aortography. J. Urol. **70:** 526, 1953.

[25] Maluf, N. S. R., and McCoy, C. B.: Translumbar aortography as a diagnostic procedure in urology with notes on caval phlebography. Am. J. Roentgenol. **73:** 533, 1955.

[26] Dos Santos, R.: Recent advances in arteriography. Lancet **2:** 482, 1941.

[27] Smith, P. G.: A résumé of the experience in the making of 1500 renal angiograms. J. Urol. **70:** 328, 1953.

[28] Koszewski, B. J., Reedy, W. J., and Iwerson, F.: Sudden death due to translumbar aortography. To be published.

[29] Robins, S. A.: Hypersensitivity to diodrast as determined by skin tests. Am. J. Roentgenol. **48:** 766, 1942.

[30] Singer, A. G., Jr.: Comparison of intradermal and ocular methods of testing for sensitivity to diodrast. Am. J. Roentgenol. **59:** 727, 1948.

[31] Keith, J. D., and Forsyth, C.: Aortography in infants. Circulation **2:** 907, 1950.

[32] Gould, D. M., and Wilson, J. K. V.: Abdominal aortography. Am. J. M. Sc. **228:** 586, 1954.

[33] McAffe, J. G., and Wilson, J. K. V.: A review of the complications of translumbar aortography. Am. J. Roentgenol. **75:** 956, 1956.

[34] Koszewski, B. J.: Diagnostic value of translumbar aortography. Thesis submitted to graduate school faculty, Creighton University, 1956.

[35] Goodwin, W. E., and Walter, R. C.: Intra-aortic procaine injection in aortography. Angiology **4:** 410, 1953.

[36] Dotter, C. T., and Steinberg, I.: Angiocardiography. Annals of Roentgenology **20:** 10–11. New York, Paul B. Hoeber Co., 1951.

[37] Harvard, M.: Renal angiography. J. Urol. **70:** 15, 1953.

[38] Wylie, E. J., and McGuinness, J. S.: The recognition and treatment of arteriosclerotic stenoses of major arteries. Surg., Gynec. & Obst. **97:** 425, 1953.

[39] Hinman, F.: A simple injector for aortography and intravenous angiography. J. Urol. **70:** 119, 1953.

[40] Langsam, M., and Wilensky, N. D.: An apparatus for automatic introduction of radiopaque media in translumbar aortography. Surgery **36:** 777, 1954.

[41] Reedy, W. J., Koszewski, B. J., and Murphy, P.: Evaluation of aortic occlusion by aortography. Ann. Int. Med. **44:** 283, 1956.

[42] Evans, A. T.: Renal arteriography. Am. J. Roentgenol. **72:** 574, 1954.

[43] Flax, N., and Waldron, R.: A syringe wired for automatic x-ray exposure. Radiology **58:** 726, 1952.

[44] Christman, F. E., and Grinfeld, D.: Simultaneous arteriography of the abdominal aorta and of the arteries of the lower extremities. Angiology **5:** 339, 1954.

[5] Johnstone, A. S.: Visualization of abdominal aorta and its branches. J. Fac. Radiologists **3:** 231, 1952.

[46] Glenn, F., Keefer, E. B. C., Speer, D. S., and Dotter, C. T.: Coarctation of the lower thoracic and abdominal aorta immediately proximal to celias axis. Surg., Gynec. & Obst. **94:** 561, 1952.

[47] Barnett, W. O., and Wagner, J. A.: Aneurysm of hepatic artery: Cause of obscure abdominal hemorrhage. Ann. Surg. **137:** 561, 1953.

[48] Abeshouse, B. S.: Aneurysm of renal artery: Report of 2 cases and review of literature. Urol. & Cutan. Rev. **55:** 451, 1951.

[49] Felson, B.: Translumbar arteriography in intrinsic disease of the abdominal aorta and its branches. Am. J. Roentgenol. **72:** 597, 1954.

[50] De Bakey, M. E., Cooley, D. A., and Creech, O., Jr.: Treatment of aneurysms and occlusive disease of the aorta by resection. J.A.M.A. **157:** 203, 1955.

[51] Estes, J. E.: Abdominal aortic aneurysm: A study of one hundred and two cases. Circulation **2:** 258, 1950.

[52] Abeshouse, B. S.: Aortography and renal arteriography following percutaneous retrograde catheterization of the femoral artery and aorta. Urol. & Cutan. Rev. **55:** 517, 1951.

[53] Lovingood, Ch. O., and Patton, H.: Translumbar aortography as a diagnostic aid in localizing arterial emboli. Arch. Surg. **67:** 164, 1953.

[54] Leriche, R.: De la resection du carrefour aorticoiliaque avec double sympathectomie lombaire pour thrombose arteritique de l'aorte; le syndrome de l'obliteration termino-aortique par arterite. Présse méd. **48:** 601, 1940.

[55] Lueth, H. C.: Thrombosis of the abdominal aorta. A report of four cases showing the variability of symptoms. Ann. Int. Med. **13:** 1167, 1940.

[56] Julian, O. C., Grove, W. J., Dye, W. S., Olwin, J., and Sadove, M. S.: Direct surgery of arteriosclerosis: Resection of abdominal aorta with homologous aortic graft replacement. Ann. Surg. **138:** 387, 1953.

[57] Rigler, L. G., and Olfelt, P. C.: Abdominal aortography for the Roentgen demonstration of the liver and spleen. Am. J. Roentgenol. **72:** 586, 1954.

[58] Milanes, B., McCook, J., and Hernandez, A. L.: Aortography and tumors of the liver. Angiology **4:** 312, 1953.

[59] Dolphin, J. A., and Williams, B.: Aortography in upper gastrointestinal hemorrhage: An experimental study. Surgery **31:** 487, 1952.

[60] Gilbert-Dreyfus, Reboul, H., and Zara, M.: Syndrome androgenique pur chez une jeune fille. Localisation par l'aortographie d'une tumeur surrenale droite. Epinephrectomie curatrice. Bull. et mém. Soc. méd. hôp. Paris, **66:** 695, 1950.

[61] Rivas, R. M.: Roentgenological diagnosis generalized subserous emphysema through a single puncture. Am. J. Roentgenol. **64:** 723, 1950.

[62] Hartnett, L.: Possible significance of arterial visualization in diagnosis of placenta previa: Preliminary report. Am. J. Obst. & Gynec., **55:** 940, 1948.

[63] Borell, U., Fernstrom, I., Lindbloom, K., and Westman, A.: The diagnostic value of arteriography of the iliac artery in gynaecology and obstetrics. Acta radiol. **38:** 247, 1952.

[64] Hamilton, G. R., Getz, R. J., and Jerome, S.: Arteriovenous fistula of renal vessels: Case report and review of literature. J. Urol. **69:** 203, 1953.

[65] Hellmer, H.: Nephrography. Acta radiol. **33:** 233, 1942.

[66] Creevy, C. D., and Price, W. E.: Differentiation of renal cysts from neoplasms by abdominal aortography: Pittfalls. Radiology **64:** 831, 1955.

[67] Goldblatt, H.: The Renal Origin of Hypertension. Springfield, Ill. Charles C Thomas, 1948.

[68] Poutasse, E. F.: Occlusion of renal artery as cause of hypertension. Circulation **13:** 37, 1956.

[69] Deterling, R. H., Jr.: Direct and retrograde aortography. Surgery **31:** 88, 1952.

[70] Wagner, F. B., Jr., and Price, A. H.: Fatality after abdominal arteriography: Prevention by new modification of technique. Surgery **27:** 621, 1950.

[71] Cournand, A., Bing, R. J., Dexter, L., Dotter, C. I., Katz, L. N., Warren, J. V., and Wood, E.: Report of committee on cardiac catheterization and angiocardiography of the American Heart Association. Circulation **7:** 769, 1953.

[72] Melick, W. F., Byrne, J. E., and Boler, T. D.: Experimental and clinical investigation of various media used in translumbar aortography. J. Urol. **67:** 1019, 1952.

[73] Baccaglini, G., and Ballarin, G.: Aortografia. Radiol. med. **27:** 1, 1940.

[74] Miller, G. M., Wylie, E. J., and Hinman, F.: Renal complications from aortography. Surgery **35:** 885, 1954.

[75] Josselson, A. J., and Kaplan, J. H.: Fatal reaction following aortography with Neo-iopax. J. Urol. **72:** 256, 1954.

[76] Fry, W. J.: Acute renal failure and death following aortography: Report of a case. Univ. Michigan M. Bull. **20:** 201, 1954.

[77] Antoni, N., and Lindgren, E.: Steno's experiment in man as complication in lumbar aortography. Acta chir. scandinav. **98:** 230, 1949.

[78] Boyarsky, S.: Paraplegia following translumbar aortography. J.A.M.A. **156:** 599, 1954.

[79] Hol, R., and Skjervan, O.: Spinal cord damage in abdominal aortography. Acta Radiol. **42:** 276, 1954.

[80] McCormick, J. G.: Paraplegia secondary to abdominal aortography. J.A.M.A. **161:** 860, 1956.

ABSTRACTS

ARTERIOSCLEROSIS

Geyer, G., Herbst, F. S. M., Thaler, H., and Lever, W. F.: The Permeability of Capillaries to Serum Cholesterol. J. Clin. Invest. **35:** 281 (Mar.), 1956.

This study was undertaken to determine to what extent cholesterol would leave the capillaries under the influence of passive congestion and whether the initial level of serum cholesterol would have an effect on the amount passing through the capillaries. A blood-pressure cuff was used to produce venous stasis, and blood samples were taken before and after congestion induced by a pressure of from 40 to 80 mm. Hg for 30 minutes. The amount of fluid lost was calculated by a change of hematocrit.

The observations reveal that under the experimental conditions described, in which there was no significant alteration in normal capillary filtration of water, no measurable amounts of cholesterol passed through the capillary wall. However, a significant relation was found to exist between the rates of fluid filtration and cholesterol filtration. The serum cholesterol levels did play some role in influencing the rate of filtration.

WAIFE

Kunkel, H. G., and Trautman, R.: The α_2 Lipoproteins of Human Serum. Correlation of Ultracentrifugal and Electrophoretic Properties. J. Clin. Invest. **35:** 641 (June), 1956.

This paper represents an attempt to define the α_2 lipoproteins in terms of both zone electrophoretic and density ultracentrifugal properties. A separate lipoprotein component in the α_2 region was observed. This ranged in concentration from 4 to 40 per cent of the total lipoproteins in the fasting serum when expressed as phospholipid. The original article should be read for details on technic.

WAIFE

Bersohn, I., and Wayburne, S.: Serum Cholesterol Concentration in New-Born African and European Infants and Their Mothers. Am. J. Clin. Nutrition **4:** 117 (Mar.–Apr.), 1956.

Determinations of the total and esterified cholesterol concentration from the serum of 51 African and 37 European mothers and their infants showed that: (1) the mean cholesterol concentrations of infants from both groups were the same; (2) the mean cholesterol concentrations in the African mothers were significantly lower than among the European mothers; and (3) no significant difference was found in the percentage of esterified serum cholesterol in the infant and maternal groups from both races.

As yet there is no adequate explanation for the lowered cholesterol concentration of the African adult. The finding that at birth there is no difference in cholesterol concentration in both European and African groups supports the view that the racial factor is not of importance in this problem. The possible effects of diet, liver disease, and sex hormones in producing the low-serum cholesterol concentration in the African adult are discussed by the authors.

SAGALL

Rinehart, J. F., and Greenberg, L. D.: Vitamin B_6 Deficiency in the Rhesus Monkey with Particular Reference to the Occurrence of Atherosclerosis, Dental Caries, and Hepatic Cirrhosis. Am. J. Clin. Nutrition. **4:** 318 (July–Aug.), 1956.

During the past 6 years, extensive studies of pyridoxine (vitamin B_6) deficiency in the rhesus monkey (Macaca mulatta) have revealed pathologic alterations suggesting that deficiency of pyridoxine may be of importance in the pathogenesis of human disease. Some 40 animals were maintained

on an essentially synthetic diet fed in tablet form containing 73 per cent sucrose, 18 per cent vitamin-free casein, 2 per cent corn oil, and the essential vitamins and minerals. Animals subjected to pyridoxine deficiency regularly develop alterations in blood vessels that bear a close similarity to arteriosclerosis as it occurs spontaneously in man. The experimental lesions are closely analogous in character and distribution to those found in man. In the experimental animals, the vascular lesions develop after 5 to 6 months of complete deprivation of this essential nutrient, with total survival time ranging from 6 to 12 months. Other pathologic changes that frequently occur are fatty metamorphosis and cirrhosis of the liver. Symptomatically the monkeys lose weight, decrease food consumption, become unkempt, sluggish, hyperirritable or apathetic, frequently develop some degree of periorbital edema, and show variable degrees of change in their fur. Laboratory studies of interest revealed the development of anemia, decrease in total leukocyte count in 50 per cent of the animals, with fall of the granulocytes and mononuclear leukocytes on peripheral smear, decreased blood B_6 and transaminase levels, and a measurable defect in tryptophan metabolism. In animals maintained for 2 years or longer on the synthetic diet and given inadequate supplements of vitamin B_6, the incidence of dental caries in the second dentition is unusually high.

Attention is called to the essentiality of vitamin B_6 in metabolism, particularly of proteins. It is problematic whether or not the average daily intake of pyridoxine in man (1.5 mg.) is adequate to meet the metabolic needs. The question arises whether or not long-term suboptimal intake of pyridoxine may be a contributory factor in the pathogenesis of the important human diseases—arteriosclerosis, dental caries, and cirrhosis of the liver

MAXWELL

BLOOD COAGULATION AND THROMBOEMBOLISM

Annotations: Pulmonary Embolism and 5-Hydroxytryptamine. Lancet **1:** 240 (Feb. 4), 1956.

Discussed is the puzzling discrepancy between the size of pulmonary emboli and the clinical signs consequent thereto. The work of Smith and Smith (Surg., Gynec. & Obst. **101:** 691, 1955) prompted the discussion. The Smiths found that the venous injection of fragments of clot formed in vitro produced much more profound effects than the injection of a suspension of starch granules. The effects of injection of multiple clot fragments resembled those of injection of 5-HT. In the animals, specific antagonists for histamine and acetylcholine made no difference in the effects of clot embolization; on the other hand, antagonists of serotonin (5-HT) profoundly diminished the effect of clot injections.

These experiments are interpreted as suggesting that release of serotonin from platelets in association with the process of embolization may play an important role in production of the clinical picture of pulmonary embolism. It was probably J. H. Comroe, Jr., who first made this suggestion (Am. J. Physiol. **171:** 715, 1952).

MCKUSICK

Rytand, D. A.: The Present Status of Anticoagulants. J. Chron. Dis. **3:** 451 (April), 1956.

Dr. Rytand discusses the differences of opinion with respect to the routine use of anticoagulants in acute myocardial infarction. In the study by the Committee on anticoagulants of the American Heart Association, the lack of complete random selection of patients in the treated and untreated groups was such that the differences in fatality rates with and without anticoagulants may have arisen from chance factors. The correction factors applied by the Committee for these factors do not completely validate the conclusions. The clinical impression of the benign course followed by "good risk" patients leaves doubt as to the value of anticoagulants in this group, while at the other extreme the "very poor risk" patients may not benefit from them. Further study on the use of anticoagulants in patients with accelerated coagulation of blood is desirable, but at present the results are questionable. The prevention of thromboembolic episodes following myocardial infarction can be reduced by anticoagulants but the increased hazard of cardiac rupture and hemopericardium must be considered. Long-term therapy with anticoagulants in prevention of myocardial infarction seems favorable but is not yet conclusively established. Multiple embolic episodes in patients with mitral stenosis and atrial fibrillation have been certainly demonstrated, including cerebral emboli, but their value in acute cerebral thrombosis is less certain. Although anticoagulants are of value in embolization, the incidence of emboli following conversion of atrial fibrillation with quinidine is so rare that anticoagulants are not indicated except in cases of repeated previous embolization. The value of heparin in acute thromboembolic phenomena is well established but that of the coumarin and indandione derivatives is much less established in comparison, both on clinical and experimental grounds. In clinical studies involving anticoagulants there must be sharp distinction between heparin and the other anticoagulant preparations.

MAXWELL

Foley, W. T.: The Present Status of Anticoagulants. J. Chron. Dis. **3:** 448 (April), 1956.

The author briefly reviews the historical aspects as well as the present uses of anticoagulants. He believes that following myocardial infarction these drugs should be used routinely when it can be done conveniently and safely with good laboratory control, for our prognostic ability is not adequate to separate initially the good risk and poor risk pa-

tients. In contrast to previous observations, Dicumarol therapy with concomitant antibiotic therapy may be indicated in subacute bacterial endocarditis to increase protection against embolization. Other indications for anticoagulants are any vascular thrombotic phenomenon including cerebral vascular thromboses to prevent the propagation of the thrombus. The choice between the various anticoagulants is an individual one, but the physician should use and become familiar with 1 drug. Moreover, constant care, testing, and watchfulness must be used when administering these drugs.

MAXWELL

Peel, A. A. F.: Selection for Anticoagulant Therapy in Cardiac Infarction using the Heparin Retarded Coagulation Time. Brit. Heart J. **18:** 378 (May), 1956.

The present paper gives the results of 4 years' experience in the use of heparin retarded coagulation time as a method for the selection of patients with acute coronary thrombosis for anticoagulant therapy.

In patients without preceding cardiovascular disease, none of the 28 with a normal time died. The mortality in those with a shortened time was reduced by anticoagulant therapy from an expected mortality of 54 per cent (as indicated by the mortality before the advent of anticoagulant therapy) to 18 per cent. Moreover, recurrences or embolism occurred within 1 year 3 times more commonly in this group than in the 1 with a normal time.

In patients with preceding cardiovascular disease, the results both of the test and of anticoagulant treatment were depressing. The death rate was not significantly affected by treatment. It was 3 times the mortality of those without preceding cardiovascular disease.

The prophylactic use of anticoagulants in patients with cardiac ischemia reduced the incidence of infarction from 11 to 7 per cent.

SOLOFF

Aya Goñi, A.: The Prevention of Embolism by Means of Permanent Anticoagulant Treatment. Rev. españ. cardiol. **9:** 445 (Dec.), 1955.

Of 100 unselected patients with mitral valvular disease, 17 had arterial embolisms; 15 of these had atrial fibrillation. Eleven cases who had a total of 19 embolisms during 1 to 14 months of observation were treated with Dicumarol and Tromexan for 6 to 52 months, keeping the prothrombin time at 30 to 60 per cent of normal. During this time only 2 embolisms occurred. No major hemorrhagic complications occurred during this time. Permanent anticoagulant treatment is recommended in all cases of pure mitral stenosis in fibrillation and in all cases of pure or combined mitral stenosis or atrial fibrillation who have a history of embolism. The treatment becomes more urgent as the age of the patient increases.

LEPESCHKIN

CONGENITAL ANOMALIES

Campbell, M., and Baylis, J. H.: The Course and Prognosis of Coarctation of the Aorta. Brit. Heart J. **18:** 475 (Oct.), 1956. Abstracted, Circulation **15:** 874 (June), 1957.

Hartleb, O.: On the Absence of Murmurs in Fallot's Tetraology. Ztschr. Kreislaufforsch. **45:** 360 (May), 1956.

In a patient in whom origin of the aorta from the right ventricle, subaortic septum defect and infundibular pulmonary stenosis were found at autopsy, no systolic murmurs could be heard or registered from any point on the anterior or posterior chest wall. Cardiac catheterization showed a systolic pressure of 130 mm. in the right ventricle and 15 mm. in the pulmonary artery. The hematocrit level was 50 per cent, the hemoglobin concentration 137 per cent. The absence of the murmur is explained by a jet effect in the extremely hypoplastic pulmonary artery that counteracts the pressure gradient at the point of stenosis and diminishes flow, and by the presence of extremely numerous intrapulmonary anastomoses.

LEPESCHKIN

Gerbode, F., Holman, E., Hultgren, H., Osborn, J. J., Purdy, A. P., Robinson, S. J., and Selzer, A.: Atypical Patent Ductus. Arch. Surg. **72:** 850 (May), 1956.

The authors described a series of 36 patients with patent ductus arteriosus in which the clinical picture was atypical. In this group there were 18 infants less than 3 years of age who had heart failure or severe symptoms. In 7 patients the patent ductus was associated with coarctation of the aorta, while in 11 it had contributed to the production of pulmonary hypertension.

The authors pointed out that in the appraisal of an infant who is showing cardiac embarrassment, the differential diagnosis is narrowed to 2 lesions; a persistent ductus arteriosus or an interventricular septal defect with a large left-to-right shunt. Retrograde arteriography was considered a worthwhile diagnostic procedure in those individuals in whom the diagnosis of patent ductus arteriosus was in doubt.

Ligation and division of the ductus arteriosus were performed in all of the infants, with clinical improvement following in every instance but 1. In those patients in whom coarctation was also present, both lesions were treated, with 1 postoperative death resulting in this group. In the patients in whom pulmonary hypertension was present, operation produced clinical improvement in 9 of 10 cases, while 1 died 9 months postoperatively.

ABRAMSON

Davis, C., Jr., Fell, E. H., Gasul, B. M., and Dillon, R.: Congenital Vascular Lesions Imitating the Patent Ductus. Arch. Surg. **72:** 838 (May), 1956.

A number of case reports of congenital malforma-

tions of the cardiovascular system were presented in which the clinical story was found to mimic that of a patent ductus arteriosus. The authors pointed out that a continuous murmur could also be present in aortic septal defect or in an aortic-pulmonary fistula. A similar type of physical finding was found in the case of an anomalous left coronary artery, shunting blood into the infundibulum of the right ventricle.

The authors suggested that if, at operation, a suspected patent ductus arteriosus is not found, one should not fail to search for some other pathologic condition, such as those already mentioned, to account for the continuous systolic and diastolic murmurs.

ABRAMSON

Amundsen, P., and Holter, I.: Cardiovascular Changes in Dystrophia Mesodermalis Congenita Marfan. Acta Radiol. **45:** 365 (May), 1956.

Case report of a 21-year-old male, tall and thin, with "spider" fingers, lack of subcutaneous tissue, poorly developed skeletal muscles, and deformed feet (all ectodermal); cardiac enlargement with predominant aortic insufficiency, BP 140/0. Electrocardiogram: left bundle-branch block and atrial fibrillation. Roentgen findings of left ventricular enlargement plus a lesser grade of left atrial enlargement. No aortic abnormalities evident. The patient died of congestive heart failure.

At autopsy the heart weighed 1000 Gm. The aortic valve was thickened and deformed. Aneurysms involving the aortic sinuses displacing the coronary ostia distally were found. No atrial or ventricular septal defects. Microscopic examination revealed the commonly found necrotic lesions, involving the media of the aorta, and to a lesser extent the medial coat of the pulmonary artery.

There was no evidence for superimposed rheumatic valvulitis; no familial history for Marfan's Syndrome.

SCHWEDEL

Dammann, J. F., Jr., and Ferencz, C.: The Significance of the Pulmonary Vascular Bed in Congenital Heart Disease. III. Defects between the Ventricles or Great Vessels in which Both Increased Pressure and Blood Flow May Act upon the Lungs and in which There is a Common Ejectile Force. Am. Heart J. **52:** 210 (Aug.), 1956.

This paper presents a correlation of the anatomic changes within the pulmonary vessels and the clinical picture in 87 patients with a common ejectile force from the heart as a result of the following malformations: ventricular septal defects, single ventricle, patent ductus arteriosus, or aortic septal defect. Theoretically, there are 3 courses that the pulmonary vascular bed may follow after birth in presence of a common ejectile force. The authors place these in 3 phases. In Phase I, following birth, the thin-walled, small-lumened, fetal pulmonary arteries thin out, the pulmonary resistance falls, the pulmonary blood flow increases, which eventually leads to high output cardiac failure. In Phase II, following birth, the fetal pulmonary arteries retain or regain their fetal state, which results in a retention of a high pulmonary resistance and a balance of the pulmonary and system circulation with minimal or absent signs and symptoms. In Phase III the fetal pulmonary arteries become narrower due to progressive medial hypertrophy and intimal sclerosis and pulmonary resistance exceeds systemic resistance with a right-to-left shunt resulting. Corrective or palliative surgery may be life-saving in Phase I, may prevent progression of pulmonary vascular changes in Phase II, and is not indicated in Phase III.

RINZLER

CORONARY ARTERY DISEASE

Jacobs, H. D., and Elliott, G. A.: Cardiac Ventricular Aneurysm in South Africa. Acta med. scandinav., Suppl. **306:** 84, 1955. Abstracted, Circulation **15:** 712 (May), 1957.

Morris, J. N., Heady, J. A., and Raffle, P. A. B.: Physique of London Busmen. Epidemiology of Uniforms. Lancet **2:** 569 (Sept. 15), 1956. Abstracted, Circulation **15:** 734 (May), 1957.

Dressler, W.: A Post-Myocardial-Infarction Syndrome. J.A.M.A. **160:** 1379 (April 21), 1956.

A complication consisting of one, or a combination of these conditions: pericarditis, pleurisy, and pneumonitis, was seen in 10 patients in a period of 13 months. In an addendum the author states that he has observed 10 more cases of this syndrome since June 1955. Prolonged or recurrent fever and pain of the pleural pericardial type are striking features. A pericardial friction rub occurs more frequently and is more often of long duration than in ordinary cases of myocardial infarction. There may be roentgenologic evidence of pleural or pericardial effusion. Cough, rales, and x-ray signs of pulmonary infiltration indicate involvement of the lungs but distinct evidence of pulmonary infarction is lacking. Leukocytosis and increase of the sedimentation rate are present in most cases. There is often a striking discrepancy between severe chest pain with fever and the scarcity of objective findings. Relapses frequently occur and prolong the febrile course of myocardial infarction by several weeks or even months. The outcome, however, has been favorable in all instances. Use of cortisone terminates fever and pain and shortens the course. The complication resembles idiopathic pericarditis and the postcommissurotomy syndrome. The etiology is unknown.

KITCHELL

Beck, C. S.: The Coronary Artery Problem. A Definition and an Answer. Geriatrics **10:** 501 (Nov.), 1955.

The problem in coronary artery disease concerns supply of red blood to the heart muscle. It has 2

components: One concerned with uniform oxygenation of the myocardium and the other with sufficient blood to keep the myocardium viable so that it can continue to contract. Experimentally, a uniform well-oxygenated or a uniformly poorly oxygenated heart is electrically stable. Where there is lack of uniformity of oxygenation there is electric instability. Two types of death occur in coronary artery disease: One in the electrically unstable heart with or without destruction of muscle and the other, failure from severe muscle damage in an electrically stable heart. One third of persons dying from coronary heart disease have an unstable heart without muscle damage, 57 per cent have an unstable heart with muscle damage, and 10 per cent have a stable heart with extensive muscle damage and die of cardiac failure.

The answer to the problem of the unstable heart lies in lessening the chance for oxygen differentials by uniformity of distribution of blood and this is to be accomplished by producing intercoronary arterial channels. The surgical procedures for accomplishing this is discussed by Beck. For example the Beck I operation has in the last 100 cases resulted in a mortality of 6 to 8 per cent, with 2 patients dying of thoracotomy alone. This operation has 4 components: (1) mechanical abrasion of the lining of parietal pericardium and surface of the heart; (2) application of an inflammatory agent to these surfaces in the form of 0.2 Gm. powdered asbestos; (3) partial occlusion of the coronary sinus to a diameter of 3 mm.; and (4) grafting parietal pericardium and mediastinal fat to the surface of the heart. The criteria for the selection of patients for operation are also considered in this article.

RINZLER

Melikova, M. Y.: Disturbances of the Cerebral Circulation during the Acute Phase of Myocardial Infarction. Klin. med. **34/4:** 23 (Apr.), 1956.

Of 130 cases of acute myocardial infarction, 41 showed neurologic symptoms such as loss of consciousness, vertigo, dizziness, convulsions, pareses, headache, etc. In some cases the cerebral manifestations may even mask the cardiac symptoms. Of 21 cases who died soon after infarction, all showed vascular changes such as vascular spasm and stasis, perivascular edema and diapedetic hemorrhages. The latter changes are considered secondary to vascular spasm with resulting anoxia, as are structural changes in the glia and nervous cells.

LEPESCHKIN

Lipetz, V. J.: Stenosing Atherosclerosis of the Coronary Arteries in Young Persons. Klin. med. **34/5:** 84 (May), 1956.

Marked stenosis of the descending branch of the left coronary artery by atherosclerotic plaques was found in a 15-year-old boy with supravalvular aortic stenosis, and in 3 men 28 to 31 years old with gastritis or gastric ulcers. All died suddenly.

LEPESCHKIN

Somoza, C., and Wilens, S. L.: Anterior and Posterior Wall Infarction of the Heart: A Statistical Comparison Based on Autopsy Findings. J. Chron. Dis. **3:** 610 (June), 1956.

The 2 most usual sites of myocardial infarction are in the anterior wall of the left ventricle near its apex and in its posterior wall close to the base. Statistical analysis of 514 cases of anterior and posterior wall infarcts of the heart revealed that the chief pathologic features of both types were similar. Anterior apical infarcts often extend to the adjacent endocardium and epicardium, and thus give rise to mural thrombus formation and pericarditis more frequently than do posterior basal ones. The differences in incidence of these complications in the 2 types of infarcts are great enough to be reasonably conclusive ones.

Differences in incidence of other characteristics are also noted but these are not of sufficient magnitude to exclude the possibility of chance variation. Some of these unproved differences would be of clinical importance if they could be confirmed by other analyses. They will, therefore, be summarized briefly. (1) The ratio of anterior wall to posterior wall infarction may increase progressively with advancing age. (2) Acute posterior wall infarction may have a slightly higher mortality rate than acute anterior wall infarction despite the lower incidence of mural thrombosis and pericarditis in the former. (3) Superimposed new infarcts in areas of old infarction may be found more frequently in the anterior wall. (4) Anterior wall infarcts in men tend to be larger than posterior wall lesions; the reverse may be true in women. (5) Healed posterior wall infarcts in women may be more often clinically manifest than other healed infarcts. (6) Thrombi in the right ventricle and both atrial appendages, as well as in the left ventricle, may less frequently complicate posterior than anterior wall infarction. (7) Preexisting hypertension may persist more frequently in acute posterior wall than in acute anterior wall infarction and may be a poor prognostic sign. (8) The coincidence of diabetes may be particularly high in fatal acute posterior wall infarction.

MAXWELL

Moeller, H. C., and Schilg, J.: Right Basal Infarction of the Heart. Ztschr. Kreislaufforsch. **45:** 206 (Mar.), 1956.

A 62-year-old man experienced sudden crushing precordial pain with radiation toward the abdomen. The electrocardiogram showed atrial fibrillation and slight elevation of S-T in leads I to III and V_6; later T became inverted in III and V_6. Autopsy disclosed aortic rupture leading to extensive periaortic hematoma with perforation into the pericardial cavity.

which contained about 400 ml. of blood. A dissecting aortic aneurysm extended to the renal arteries. Fresh myocardial infarction of the right atrium and the posterior wall at the base of the right ventricle and septum was found. There was extensive coronary sclerosis but no occlusion, and the infarction is attributed to compression of the right coronary ostium by the hematoma.

LEPESCHKIN

Osburg, K.: A Case of Myocardial Infarction Due to Tamponade of a Coronary Ostium by an Isolated Aortic Thrombus. Ztschr. Kreislaufforsch. **45:** 192 (Mar.), 1956.

Massive infarction of the anterior and posterior walls of the left ventricle resulted from impaction of a pedunculated aortic thrombus into the ostium of the left coronary artery. The thrombus originated in a small atheromatous erosion immediately above the ostium. Other sections of the aorta and the coronary arteries showed no significant atheromatous changes.

LEPESCHKIN

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Doll, E.: The Upper Turning Point in Precordial Leads of the Normal Newborn, Its Evolution During the First Months of Life and Its Relation to the Vectorcardiogram. Ztschr. Kreislaufforsch. **45:** 210 (Mar.), 1956.

In 149 normal infants the difference in the time of appearance of the "upper turning point" (apex of R) in the synchronously registered leads V_1 and V_6 taken at quadruple velocity was -0.0032 sec. in the first week of life (i.e., the apex of R was earlier in V_6). It was -0.0015 sec. in the second week, -0.00025 in the third week, $+0.0020$ in the fourth week, $+0.0056$ in the second month, and $+0.0067$ in the third month. Whenever the difference was negative or near zero, the QRS vectors in the horizontal vectorcardiogram (cube system) showed clockwise rotation; whenever it was positive, the QRS loop showed counterclockwise rotation. The minimal values for the difference were -0.005 sec. for the second through fourth week, -0.004 sec. in the second, and 0 in the third month.

LEPESCHKIN

Bakulev, A. N., Babski, E. B., and Karpman, V. L.: Efficacy of Surgical Treatment of Mitral Stenosis in the Light of Cardiohemodynography. Klin. med. **34/5:** 36 (May), 1956.

The cardiohemodynomogram (similar to the ballistocardiogram) after successful mitral commissurotomy is characterized by shortening of intervals corresponding to the isometric phase of contraction and return to a more normal configuration. Less constant is shortening of the atrial systole and prolongation of the ventricular ejection phase.

LEPESCHKIN

Nicolai, W., and Gadermann, E.: A Method of Transmission and Permanent Recording of Biological Data (Biophonar Method). Ztschr. Kreislaufforsch. **45:** 293 (Apr.), 1956.

A portable single-channel modulator weighing only 5.5 Kg. was constructed, which enables the transmission of electrocardiograms, pulse waves, and phonocardiograms over commercial telephone and radio circuits by frequency modulation of a 5000 cps acoustic carrier wave. The frequency range is zero to 150 cps for electrocardiograms, 20 to 800 cps for heart sounds. A larger instrument, provided with a cathode ray oscilloscope, was constructed for simultaneous transmission of 2 channels, using 2 frequency bands. All data can be registered and stored on magnetic tape.

LEPESCHKIN

Lac, H., Feinberg, A. W., and Cohen, B. M. Studies of the Arterial Pulse Wave. J. Chron Dis. **3:** 618 (June), 1956.

A sensitive instrument for the recording of arterial pulse waves was described. It was tentatively designated as a Vasculograph. The characteristics of the normal arterial pulse wave contour, as recorded by this instrument, were reported. The accuracy of the recordings was demonstrated by the similarity of simultaneous intraarterial and extraarterial tracings. The changes in configuration of the arterial pulse wave in the presence of clinical evidences of arteriosclerosis appeared to be diminution to disappearance of the dicrotic wave. The accuracy of this finding was also demonstrated by simultaneous intraarterial and extraarterial recordings. The implications of the disappearance of the dicrotic wave in the presence of clinical evidences of arteriosclerosis were discussed. One hypothesis was that increased "tonus" of the vascular wall may abolish the dicrotic wave.

MAXWELL

Siciliano, L.: Toward Greater Precision in Scientific Terminology with Reference to the Electrocardiogram. Cuore e circolaz. **40:** 51 (Feb.), 1956.

The term "spike" is considered better suited for the Q, R, and S waves, which do not show wave form. "Upward" or "downward" deflections are considered better terms than "positive" and "negative." It is considered illogical to call a negative deflection a Q or S wave if it corresponds in time to a tall R wave in another lead; it is preferable to call Q the initial, R the middle, and S the terminal part of the initial complex, or to designate the waves of each lead with plus or minus signs, followed by their respective potentials.

LEPESCHKIN

Cardi, L.: Functional Changes of the Heart During Hypothermia. An Electrocardiographic Study. Angiology **7:** 171 (Apr.), 1956.

Electrocardiographic and phonocardiographic tracings were obtained in 10 dogs in whom hypothermia had been induced. All phases of cardiac activity were prolonged. The most marked changes were the slowing of the rate and the increased duration of ventricular systole.

WESSLER

Testoni, F., Tommaselli, A., and Semeraro, S.: The Electrocardiogram in Myocardial Infarction. Cuore e circolaz. **40:** 1 (Feb.), 1956.

On the basis of analysis of 246 cases with serial electrocardiograms, several types of QRS changes are recognized. A QS pattern appears in V_1 to V_3 in anterior and in the dorsal lead in posterior infarction; this is accompanied by the reciprocal pattern of a pure R wave or a taller-than-usual R wave in leads from diametrically opposed regions. A polyphasic mainly negative QRS of low voltage is found in leads V_5 to V_7 in lateral infarction; a corresponding reciprocal mainly positive pattern appears in this case in lead aV_R. A QS pattern or its reciprocal pure R pattern was found in lateral infarction only if this was accompanied by conduction disturbances in the right ventricle. The rarity of the QS pattern in lateral infarction is ascribed to the fact that the forces produced by activation of the anterior and posterior walls are normally counterbalanced by corresponding forces in the opposite wall while those produced by activation of the lateral wall and apex are not. The reciprocal depression of S-T in leads on the opposite body surface is much less pronounced than the reciprocal elevation of R in the same leads. Three types of T-wave changes are differentiated. The first includes changes secondary to intraventricular conduction disturbances. The second type is characterized by inversion of T with pointed apex and symmetrical limbs, always accompanied by prolongation of Q-T; the amplitude of these T waves is inversely proportional to that of the S-T elevation. This type is attributed to gradual recovery of partly injured marginal muscle; it cannot be due to ischemia, as it would then be maximal in the initial phase of infarction. The third type consists of inversion of T with rounded apex and low voltage, persisting long after the infarction and not accompanied by prolongation of Q-T; it is attributed to unopposed repolarization potentials of the opposite wall of the ventricle. The mean duration of the first phase of infarction (elevated S-T and T) was the first 3 days, that of the second phase (elevated S-T, inverted T) was the following 30 days, that of the third phase (inverted T) was the following 90 days. The duration was longer in anterior and shorter in posterior infarction patterns.

LEPESCHKIN

Martín de Prados, B.: The Ballistocardiogram after Mitral Commissurotomy. Rev. españ. cardiol. **9:** 355 (Oct.), 1955.

The most important ballistocardiographic sign of mitral stenosis is an increase in the amplitude of the L and N waves. This increase was found to develop in 1 case toward the end of pregnancy, while in another it was accentuated during inspiration. It was attributed to increased force of venous filling of the left ventricle. It disappeared after commissurotomy, but gradually reappeared in several cases presumably because of reappearance of valvular stenosis.

LEPESCHKIN

Borchard, F., and Cornu, C.: Cardiac Catheterization in Infants. Arch. mal. coeur **49:** 169 (Feb.), 1956.

Catheterization was made with a number-6 Cournand catheter, using the right femoral vein; after ligation of the vein, cyanosis and edema of the leg usually persisted for 48 hours. 0.04 Gm. per Kg. Gardenal was given in 3 doses during the 24 hours preceding the examination. Infection and hyperthermia should be avoided. If 3 or 4 samples of blood are necessary, a blood transfusion is recommended. Right ventricular pressures were similar to those of adults. Catheterization should not be made if the electrocardiogram shows signs of myocardial ischemia or in the presence of infections or digestive disturbances.

LEPESCHKIN

Angebrand, W., and Moll, A.: The Aortic Electrokymogram in Persons with Normal Hearts and in Cardiacs with Aortic Insufficiency. Arch. Kreislaufforsch. **23:** 282 (Dec.), 1955.

The isometric contraction phase (measured from the apex of R in the electrocardiogram to the beginning of the rapid ascent in the electrokymogram of the aortic knob, less 0.05 second for the "response time of the photocell") averaged 0.08 second for 23 normal persons and 0.06 second for 23 persons with aortic regurgitation. It was especially short in advanced cases. The values tended to be slightly lower at high heart rates. The duration of the ascent (rapid ejection) rose with falling heart rate, and averaged 0.16 sec. in normal persons and 0.19 second in aortic regurgitation. The interval from apex to the incisura (slow ejection) averaged 0.08 second independently of the heart rate, and was prolonged in mild aortic regurgitation. The diastolic interval showed the greatest dependence of the heart rate; it was shorter in aortic regurgitation. In these cases the incisura tended to appear lower down on the descending branch and to become less pronounced; it was absent in all advanced cases.

LEPESCHKIN

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Belli, J., and Waisbren, B. A.: The Number of Blood Cultures Necessary to Diagnose Most Cases of Bacterial Endocarditis. Am. J. M. Sc. **232:** 284 (Sept.), 1956.

The records of 82 bacteriologically proved cases of subacute bacterial endocarditis were examined to determine the number of blood cultures necessary to obtain a positive result. Seventeen cases of established subacute bacterial endocarditis having repeated sterile cultures were analyzed for comparison with the first group. In 77 of the 82 cases with positive cultures the causative organisms were found within the first 5 cultures. Fifty-two were diagnosed by the first culture drawn. In no cases were more than 10 cultures necessary to make the diagnosis. The results of this study indicate that after 5 sterile blood cultures are obtained there is a decreasing possibility of making a bacteriologically proved diagnosis of subacute bacterial endocarditis. Although it is desirable to obtain an etiologic agent in a given case of endocarditis, it is justifiable to begin therapy in order to reduce valve damage and other complications of this disease under these conditions.

SHUMAN

Reid, E. A. S., Hutchison, J. L., Price, J. D. E., and Smith, R. L.: Idiopathic Pericarditis. Ann. Int. Med. **45:** 88 (July), 1956.

Twenty-three cases of idiopathic pericarditis are presented. The criteria for the selection of these cases were based on the presence of pain, a pericardial friction with or without a characteristic electrocardiographic configuration, and the absence of any specific demonstrable cause for the pericarditis. The disease predominantly affected young adult males. The pericardial friction rub is the most important physical sign. Fever, tachycardia, pleuritis, and pneumonitis can also be present. In 3 of the patients pericardial paracentesis was done. Moderate grades of leukocytosis and acceleration of the erythrocyte sedimentation rate were frequently present. Electrocardiographic alterations are especially important. The changes in serial electrocardiograms can serve to confirm the diagnosis. Review of the literature indicates that various possible causes operate to produce the syndrome of idiopathic pericarditis. No single cause can definitely be incriminated. The diagnosis of idiopathic pericarditis is established by the exclusion of specific forms of pericarditis and by the exclusion of other diseases that cause thoracic and abdominal pain. The differential diagnosis between idiopathic pericarditis and myocardial infarction is especially important. The diagnosis of idiopathic pericarditis is frequently overlooked in patients of advanced years. There is no specific therapy. Usually, the prognosis is good. Complete recovery can be expected but in 35 per cent of the present series of patients recurrence of the disease developed. In the present series, 1 case terminated in death, representing the fourth such case described in the literature. In the presence of signs of cardiac tamponade, pericardial paracentesis is a very important procedure and can be life saving.

WENDKOS

Berk, M.: Carcinomatous Involvement of the Pericardium Producing the Syndrome of Constrictive Pericarditis: Report of a Case. Ann. Int. Med. **45:** 298 (Aug.), 1956.

Involvement of the pericardium in the course of generalized carcinomatosis is not uncommon. The production of the syndrome of chronic cardiac compression, namely constrictive pericarditis, as a result of the malignant process is, however, infrequent. To the small number of reported cases, a new such case is added. The patient presented clinically the picture of chronic constrictive pericarditis. In many respects the clinical picture resembled that resulting from chronic tuberculous disease of the pericardium. The malignant character of the condition was not discovered until thoracectomy demonstrated presence of a tumor that had invaded surrounding structures. The origin of the carcinoma was in the bronchus. Because of the rising incidence of bronchogenic carcinoma with its multiple manifestations, constrictive pericarditis secondary to this lesion can be expected to become more frequent. As a consequence it will be necessary for clinicians to consider metastatic malignancy as an additional cause of chronic constrictive pericarditis.

WENDKOS

Andreassen, R., and Jensen, N. K.: Bacterial Endocarditis Following Mitral Valvotomy. Ann. Int. Med. **45:** 534 (Sept.), 1956.

The authors discuss a patient in whom bacterial endocarditis followed cardiac catheterization and mitral commissurotomy. The first symptoms of the endocarditis appeared 29 days after the commissurotomy. The infective organism recovered from 5 separate blood cultures was a *Staphylococcus albus* which was hemolytic, coagulase negative and extremely resistant to penicillin. It was most sensitive to neomycin, oxytetracycline, chlortetracycline, and erythromycin. It was less sensitive to carbomycin, bacitracin, and streptomycin. A regimen of treatment with intravenous erythromycin and intramuscular streptomycin for 4 weeks produced prompt response. A follow-up study indicated that the patient was in a good state of health 1 year after therapy. The high blood levels of erythromycin resulting from intravenous administration may produce better results than have been obtained in the past with oral therapy. In view of the poor results with erythromycin alone in bacterial endocarditis and the

rapid emergence of resistant organisms, particularly staphylococci, it should not be used unless the organisms are highly resistant to penicillin and highly sensitive to erythromycin, and should then be used only in combination with other antibiotics, notably streptomycin and bacitracin. Further trials are needed to decide whether such combined erythromycin therapy is as effective as the broad spectrum antibiotics in penicillin resistant, staphylococcic endocarditis.

WENDKOS

Dalton, J. C., Pearson, R. J., Jr., and White, P. D.: Constrictive Pericarditis: A Review and Long-Term Follow-Up of 78 Cases. Ann. Int. Med. **45:** 445 (Sept.), 1956.

This article represents the fourth report from the Clinic of the Massachusetts General Hospital in which a large number of patients with chronic constrictive pericarditis are described. The total series consists of 78 cases, 63 of whom underwent corrective surgery. Forty-two of these 63 patients are still living. Six have been under continuous observation for more than 20 years. These 6 patients are living normal, unrestricted lives. Excellent results were obtained in 32 patients who underwent surgery. In 14, the results were fair. Five were not benefited. Six patients died from complications. There were 7 operative deaths. The signs indicative of constrictive pericarditis included abdominal swelling, distention of the cervical veins, and varying degrees of peripheral edema. Dyspnea was common. Abnormal T-waves were noted in all instances. In a majority of the patients, no changes in the electrocardiogram occurred postoperatively. A systolic blood pressure above 130 mm. Hg was found in only 1 patient preoperatively, whereas wide pulse pressures were not rare. Cardiac enlargement was present in one half the cases. Cardiac pulsations were diminished in four fifths of the cases but were fluoroscopically normal in the other fifth. Atrial arrhythmias were common, having been found in 34 of the 78 cases. Calcification was noted in the pericardium in 60 per cent of the cases. When the etiology was unequivocal, it was invariably tuberculous. One patient did not develop symptoms until the age of 78. For this reason, congestive failure in elderly patients need not always be assumed to be secondary to arteriosclerotic heart disease. The diagnosis of constrictive pericarditis can be established unequivocally by means of cardiac catheterization. The characteristic findings include (1) moderately low resting cardiac output (2) elevated pulmonary capillary pressure (3) a characteristic early diastolic dip and plateau pattern in the right ventricular pressure tracing (4) elevated and relatively uniform pulmonary wedge, pulmonary artery diastolic, right ventricular end-diastolic, right atrial, and vena caval pressures.

WENDKOS

HYPERTENSION

Trishina, A. A.: Hyperthermia in Hypertensive Disease. Klin. med. **34/5:** 80 (May), 1956.

Of 134 hypertensives free from infections, subfebrile resting temperatures were found in one-half of those in the first phase of the disease, one-sixth of those in the second phase and one-fourth of those in the third phase. During normal work hyperthermia was much more common in hypertensive than in nonhypertensive subjects of the same age and under the same conditions. The temperature changes of 1 leg after application of heat or cold to the other leg were also more pronounced or paradoxical in hypertensive patients.

LEPESCHKIN

Kushky, R. O.: The Syndrome of Right Ventricular Failure in Hypertensive Disease. Klin. med. **345:** 52 (May), 1956.

Seven cases of hypertensive disease were observed in which signs of right ventricular failure appeared before those of left ventricular failure; this was caused by compression of the right ventricle by the hypertrophic left ventricle, which was verified at autopsy in all cases. Marked left ventricular hypertrophy together with right atrial dilatation was a diagnostically useful x-ray sign.

LEPESCHKIN

Roantree, R. J., and Miller, M. R.: The Treatment of Severe Arterial Hypertension with Pentolinium. J. Chron. Dis. **3:** 597 (June), 1956.

Eight cases of severe hypertension treated with pentolinium (orally) were presented. All the patients had retinal hemorrhages or exudates and proteinuria; 4 were in congestive heart failure; and 3 had serum creatinine levels of over 2.0 mg. per 100 ml.

For initial therapy, the patients were usually hospitalized, so that the rare causes of hypertension might be excluded, and so that the dose of pentolinium might be increased more rapidly than would be possible with less frequent observation. Because reserpine was reported to potentiate the response to pentolinium and to eliminate some of the wide swings of pressure induced by the latter, it was included in most treatment schedules. Following discharge the patients were followed on an out patient basis from 3 times a week to 1- or 2-week intervals, and for psychologic reasons, were not requested to take their own blood pressures at home.

Treatment was discontinued in 1 patient because of the unpredictability of hypotensive response. A cerebrovascular accident discouraged treatment in a second case. Six are continuing treatment. Among these all showed clearing of retinal hemorrhages. Papilledema cleared in the 3 cases in which it had been present. Three of 4 patients showed disappearance of the signs of heart failure while on anti-

hypertension drugs alone, and the fourth showed improvement, but this may have been primarily due to digitalis. The renal status and electrocardiographic pattern stayed essentially constant in all patients. Most of the patients in this series had severe hypotensive reactions at one time or another. Unpleasant drug effects other than the hypotensive one caused no discontinuance of treatment although all patients experienced such effects to a variable degree. Side effects included loss of potency in every male patient; loss of accommodation, corrected by use of positive lenses; constipation, usually well controlled by the use of milk of magnesia; and the patients accustomed themselves well to the dry mouth, feelings of chilliness, and the sitting posture during the night. No urinary symptoms were noted.

MAXWELL

Green, R. S., and Davolos, D.: A Long-Term Study of the Effect of Crude Rauwolfia Serpentina and of Its Alseroxylon Fraction in Patients with Hypertension. Am. J. Med. **20:** 760 (May), 1956.

The effect of crude Rauwolfia or its alseroxylon fraction was studied in 40 patients with hypertension in whom a safe reduction of blood pressure was clinically desirable. The results indicate that *Rauwolfia serpentina* derivatives, such as rauwiloid, offer a useful therapeutic approach in patients with hypertension. Approximately half of the patients with complicated hypertension and persistently elevated diastolic pressures responded favorably, both subjectively and objectively. Good subjective improvement was seen in virtually every case whether or not a hypotensive response was obtained. Sedation, even to the point of apathy, lack of ability to concentrate, nightmares and nasal congestion were the principal undesirable side effects that necessitated a reduction of dosage. Unfavorable effects on the cardiovascular system or cerebral, renal, hepatic or blood functions were not observed. A significant difference in response between white and Negro patients indicates that this racial factor should be considered in any study of hypotensive agents. White patients with enlargement of the left ventricle, and associated coronary disease, did better than Negro patients with an enlarged left ventricle and without coronary artery disease. In general, the white patients showed a better blood pressure drop than Negro patients. There was also a significantly higher frequency of cerebral complications in Negro patients as opposed to white patients. Coronary artery disease occurred significantly more often in white patients than in Negroes.

HARRIS

Poumailloux, M., Callerot, L., and Granier, J.: Critical Study of the Hydrazinophthalazines. Arch. mal. coeur **49:** 351 (Apr.), 1956.

In 15 hypertensive persons, 1,4-dihydrazinophthalazine (Nepressol) was given orally in tolerance doses (100 to 1200 mg.). Prior to treatment bed rest was instituted for 6 to 8 days, and blood pressure determination was made always under the same conditions. Five patients showed a considerable fall of average systolic and diastolic pressures, improvement of ocular fundus abnormalities and complete disappearance of subjective symptoms without side reactions. Four cases experienced no change; 3 of these had renal involvement while 1 had aortic coaretation. In 6 cases symptoms of intolerance (tachycardia, headaches, tremor, or nausea) prevented effective dosage.

LEPESCHKIN

METABOLIC EFFECTS ON CIRCULATION

Bergy, G. G., Burroughs, R. W., and Bruce, R. A.: Effects of Cortisone on Metabolic Responses in Myocardial Infarction. Am. J. M. Sc. **232:** 513 (Nov.), 1956. Abstracted, Circulation **15:** 896 (June), 1957.

Hamwi, G. J., and Brown, D. B.: The Effects of Carbonic Anhydrase Inhibitor in Addison's Disease. Arch. Int. Med. **97:** 778 (June), 1956.

The carbonic anhydrase inhibitor acetazoleamide (Diamox) was given to 5 patients with adrenal insufficiency in order to determine possible interrelations between the action of carbonic anhydrase and the adrenal cortical steroids on renal tubular function. In 4 of the patients the administration of acetazoleamide resulted in an increase in the urinary volume and total excretion of sodium, potassium, and chloride. The fifth patient showed an increased urinary volume with no significant change in the electrolytes. Four of the 5 patients manifested symptoms of early adrenal crisis 12 to 36 hours after administration of the acetazoleamide. The patients responded rapidly to replacement therapy. Two of the patients were given acetazoleamide after they had been placed on maintenance steroid therapy. While showing the same urinary and electrolyte response, they did not manifest any untoward clinical signs or symptoms.

These results indicate that the carbonic anhydrase mechanism can operate in the absence of physiologic amounts of adrenal hormones and that the ion-exchange mechanism in the kidney affected by the adrenal steroids can operate in the presence of acetazoleamide. The possibility of using acetazoleamide as an indirect test of the salt-retaining activity of the adrenal cortex is presented.

BERNSTEIN

Vanamee, P., Poppell, J. W., Glicksman, A. S., Randall, H. T., and Roberts, K. E.: Respiratory Alkalosis in Hepatic Coma. Arch. Int. Med. **97:** 762 (June), 1956.

Twenty-five of 29 patients in hepatic coma had respiratory alkalosis and a coincident elevation of blood ammonia. No correlation between blood

ammonia levels per se and the symptomatology of hepatic decompensation was evident in the patients studied.

It has been suggested that ammonia may stimulate respiratory exchange and lead to respiratory alkalosis in patients with severe liver failure and that the physiologic alterations resulting from respiratory alkalosis may be added to the toxic effect of ammonia.

BERNSTEIN

Meyer, J., and Bow, T. M.: Effect on Cardiac Glycogen of Intravenously Administered Sodium Acetoacetate-3-C^{14}. Proc. Soc. Exper. Biol. & Med. **91:** 610 (April), 1956.

In dogs made diabetic by pancreatectomy, the glycogen content of liver and skeletal muscle decreases while that of cardiac muscle increases. A similar pattern has been observed in rats injected with large amounts of acetoacetate. The injection of large amounts of C^{14}-labeled acetoacetate did not result in the storage of radioactive cardiac glycogen. It thus appears that the net increase in heart carbohydrate accompanying ketonemia represents some secondary and yet undetermined influence of ketone bodies.

AVIADO

Bentley, W. B. A., and Van Itallie, T. B.: Metabolic Effects of Fat Emulsions Administered Intravenously to Human Subjects. J. Lab. & Clin. Med. **48:** 184 (Aug.), 1956.

Studies on the metabolic effects of 15 per cent fat emulsions administered intravenously to 4 healthy volunteer subjects maintained on constant diets inadequate in calories and adequate in protein are described. The control and experimental periods were each of 5 to 7 days' duration in all subjects. In 3 of the subjects, the negative nitrogen and potassium balances produced by caloric privation were significantly decreased when intravenous fat emulsions providing approximately 1,200 to 1,400 calories per day were administered as caloric supplements. In every instance, the potassium balances responded more dramatically to intravenous fat administration than did the nitrogen balances. The fourth subject developed diarrhea during the period of intravenous fat administration, and the augmentation of the nitrogen and potassium losses that ensued masked any significant changes that might have occurred. Similarly, in this subject, marked constipation, which occurred during the second control period, made interpretation of the results difficult. Two of the subjects were also given supplementary oral fat in amounts similar to the amounts supplied by the intravenously administered fat. Generally, the results obtained when oral fat was given were comparable to those observed when the same amount of supplementary fat was administered intravenously. These studies constitute further evidence that suitably prepared intravenous fat emulsions administered to human subjects are utilized for calories and can decrease nitrogen and potassium deficits induced by diets inadequate in caloric content.

MAXWELL

PHARMACOLOGY

Denison, A. B., Jr., Bardhanabaedya, S., and Green H. D.: Adrenergic Drugs and Blockade on Coronary Arterioles and Myocardial Contraction. Circulation Research **4:** 653 (Nov.) 1956. Abstracted Circulation **15:** 864 (June), 1957.

Heymans, C., de Schaepdryver, A. F., and King T. O.: Carotid Sinus Baroreceptors and Adrenalin Hypertension. Arch. internat. pharmacodyn. **107** 479 (Sept.), 1956. Abstracted, Circulation **15:** 91 (June), 1957.

Perlmutter, M.: Rapid Test for Adrenocortical Insufficiency. J. A. M. A. **160:** 117 (Jan. 14), 1956. Abstracted, Circulation **15:** 517 (April), 1957.

Shapiro, A.: Consideration of Multiple Variables in Evaluation of Hypotensive Drugs. J.A.M.A. **160:** 30 (Jan. 7), 1956. Abstracted, Circulation **15:** 567 (April), 1957.

Freedman, A. L., Barr, P. S., and Brody, E. A.: Hemolytic Anemia Due to Quinidine: Observations on its Mechanism. Am. J. Med. **20:** 806 (May), 1956.

A case is described in which the therapeutic administration of quinidine sulfate was associated with the acute occurrence of both thrombocytopenic purpura and hemolytic anemia. Both processes subsided within 1 week after withdrawal of the drug. Immune mechanisms were demonstrated both in relation to the thrombocytopenic purpura and to the hemolytic anemia. The patient's serum contained a factor that, in the presence of quinidine, caused hemagglutination of all red cells tested and that caused hemolysis when complement was present. Blood concentrations of quinidine attained with therapeutic doses of the drug were capable of activating the hemolytic system. The levo-isomer of quinidine and other agents did not do so. The serum factor was present in high concentration initially, and a significant titer was still present 140 days after the clinical reaction. The factor was stable, migrated electrophoretically with gamma globulin and was adsorbed onto red blood cells in the presence of quinidine. Complement was required and was fixed in the lytic reaction. The serum factor was defined as an antibody and the hemagglutinating-hemolytic reactions as immunologic. The combination of erythrocyte-quinidine antibody was an extremely loose one, suggesting a possible explanation for the rarity of reports of hemolytic anemia due to quinidine. Hemolytic anemia and hematocytopenia may be shown to be due to other drugs by in vitro methods and thus spare the patient the obvious risk of a test dose or repeat course of the medication.

HARRIS

McCubbin, J. W., Gardner, W. J. and Page, I. H.: Effect of Carotid Sinus Denervation on Arterial Pressure Response to Tetraethylammonium Chloride in Normotensive Man. Am. J. M. Sc. **232:** 297 (Sept.), 1956.

While section of the carotid sinus and aortic depressor nerves produces chronic hypertension in experimental animals, section of the carotid sinus nerves alone does not. The latter procedure does result in a pronounced increase in the response to hypotensive agents such as tetraethylammonium chloride, pentomethonium, and hydrazinophthalazine. In the present study, 4 patients with bilateral carotid sinus denervation used in treatment of progressive muscular dystrophy were examined following injection of tetraethylammonium chloride in order to examine the depressor responsiveness in man after this procedure. It was found that the responses to this agent were much enhanced after carotid sinus denervation. Repetitive administration of tetraethylammonium chloride elicited repeated large depressor responses instead of the usual gradual diminution and reversal of response.

SHUMAN

Haley, T. J., and McCormick, W. G.: Comparison of the Effect of Ergotamine and Hydergine on Muscle and Skin Blood Flow in the Anesthetized Dog. J. Pharmacol. & Exper. Ther. **117:** 406 (Aug.), 1956.

The ergot alkaloids had little or no effect on the dilator response to ischemia, and a slight reduction of the vasodilatation produced by Methacholine. Both alkaloidal preparations had a 2-fold effect on the blood vessels, causing either constriction or dilatation depending on the dose injected. Higher doses caused dilatation. Although ergotamine caused reversal of epinephrine constriction in the muscle, Hydergine was ineffective, which is probably related to its potent primary dilator effect.

AVIADO

Ross, C. A., and Herczeg, S. A.: Protective Effect of Ganglionic Blocking Agents on Traumatic Shock in the Rat. Proc. Soc. Exper. Biol. & Med. **91:** 196 (Feb.), 1956.

Pretreatment with ganglion-blocking agents (hexamethonium, chlorisondamine, mecamylamine, pentolinium) produced significant protection from the mortality of drum trauma. This finding provides additional support for the observation that blockade of the sympathetics during physical assault prevents shock. The role of the parasympathetic division is more difficult to assess, since the well-characterized cholinergic blocking agents produce some degree of autonomic ganglionic blockade. It is suggested that the protective effect of large doses of atropine and of local anesthetics may well be the result of sympathetic ganglionic blockade.

AVIADO

Horvath, S. M., Spurr, G. B., and Blatteis, C.: Effect of Chlorpromazine on Survival from a Single Massive Hemorrhage. Am. J. Physiol. **185:** 505 (June), 1956.

When chlorpromazine (2 or 5 mg./Kg.) was administered 5 hours before a hemorrhage equal to 4 per cent of body weight there was no change in survival. However, if either dose was given one half hour before hemorrhage or the smaller one immediately after, a deleterious effect was exerted on survival. It is suggested that the autonomic blocking action of chlorpromazine may explain the reduced frequency of survival.

OPPENHEIMER

PHYSICAL SIGNS

Samet, P., and Anderson, W.: Pendular Motion of the Mediastinum. Am. J. Med. **20:** 860 (June), 1956.

Five types of mediastinal respiratory shift have been observed in 21 patients. In types 1 and 2 the mediastinum is midline on expiration but is displaced to one side during inspiration. In type 2 these findings are noted both on fluoroscopy and on x-ray; in type 1 the shift is usually not seen on x-ray. In type 3 the mediastinum is displaced to one side on expiration and to the opposite side during inspiration. In type 4 the mediastinum is midline on inspiration but is displaced toward the normal side on expiration. In type 5 the mediastinum is pulled into the diseased side during both phases of respiration as a result of complete endobronchial occlusion.

HARRIS

Dock, W.: Loud Presystolic Sounds over the Jugular Veins Associated with High Venous Pressure. Am. J. Med. **20:** 853 (June), 1956.

A loud presystolic gallop sound can usually be recorded from the areas over the jugular veins of patients with acquired or congenital heart disease when they have sinus rhythm and elevated levels of pressure in the right atrium. This sound, maximal 0.10 to 0.16 second after the onset of P, is either absent or barely apparent in traces taken from the precordium. This sound occurs close to the peak of the jugular "a" wave. Patients with very loud fourth sounds from the jugular vein often have very large presystolic headward or rightward gallop waves in the ballistocardiogram. These presystolic phenomena are believed due to a wave of blood moving violently centrifugally at the height of atrial systole when there is high pressure in the right ventricle at the end of diastole or when there is tricuspid stenosis as in 2 patients in this series.

HARRIS

Myers, J. D., Murdaugh, H. V., McIntosh, H. D., and Blaisdell, R. K.: Observations on Continuous Murmurs over Partially Obstructed Arteries. Arch. Int. Med. **97:** 726 (June), 1956.

A patient with the aortic arch syndrome with a continuous bruit at the base of the neck anteriorly is presented, and the 8 previously observed patients with such bruits are reviewed. A similar murmur can be produced experimentally in dogs by partial arterial occlusion under circumstances where collateral arterial bypass is prohibited. In a patient with occlusive arterial disease, a systolic femoral artery murmur was converted into a continuous murmur by local exercise. The mechanisms involved in these phenomena are discussed, and it is concluded that a continuous murmur can occur with partial arterial occlusion under circumstances where collateral circulation is inadequate to provide a satisfactory diastolic pressure distal to the occlusion. The absence of adequate arterial collateral circulation usually means that all or most of the large arteries of the region involved are severely diseased.

BERNSTEIN

Olesen, K. H., and Warburg, E.: Fourteen Cases of Loud Apical Systolic Murmurs in Patients under 30 Years (A follow-up Study). Acta. cardiol. **11:** 165 (Fasc. 2), 1956.

The authors report a follow-up study extending over 6 to 20 years on 14 patients with isolated grade III systolic apical murmurs, all less than 30 (average 18.6) years old at the time of detection of the murmur. Eleven of these patients had had rheumatic fever before the examination and, of these, 3 developed aortic stenosis, 2 in combination with a mitral valvular lesion. None of the patients without a history of rheumatic fever developed valvular disease. No patient developed heart failure or died during the period of observation. The authors conclude that in general a patient with a loud systolic apical murmur has a very favorable prognosis.

PICK

Gray, I. R.: Paradoxical Splitting of the Second Heart Sound. Brit. Heart J. **18:** 21 (Jan.), 1956.

Closure of the aortic valve normally precedes that of the pulmonary valve. Splitting of the second sound to the left of the sternum is normal during inspiration due to the prolongation of right ventricular systole.

Paradoxical splitting or a decrease or abolition of splitting during inspiration was heard and confirmed by phonocardiography in 18 subjects with left bundle-branch block, 10 with aortic stenosis, 10 with patent ductus arteriosus, 1 with mitral stenosis, and 1 with hypertension. Paradoxical splitting in mitral stenosis and hypertension is exceptional. In left bundle-branch block, it is due to a delay in onset of ventricular activation. In aortic stenosis, it is due to a prolongation of left and a shortening of right ventricular systole, and is a sign of severe stenosis. In patent ductus arteriosus, the mechanism is similar to that of aortic stenosis. It occurred only when there was a substantial left-to-right shunt with some elevation of the pulmonary artery pressure.

SOLOFF

PHYSIOLOGY

Clemedson, C.-J.: Blast Injury. Physiol. Rev. **36:** 336 (July), 1956. Abstracted, Circulation **15:** 902 (June), 1957.

Rotta, A., Cánepa, A., Hurtado, A., Velásquez, T., and Chávez, R.: Pulmonary Circulation at Sea Level and at High Altitudes. J. Appl. Physiol. **9:** 328 (Nov.), 1956. Abstracted, Circulation **15:** 769 (May), 1957.

Brind, S. H., Bianchine, J. R., and Levy, M. N.: Effect of Bilateral Occlusion of Common Carotid Arteries on Cardiac Output and Oxygen Content of Arterial and Venous Blood in the Anesthetized Dog. Am. J. Physiol. **185:** 484 (June), 1956.

Bilateral carotid occlusion did not alter cardiac output. Vasomotor tone was increased. Arterial oxygen content, venous oxygen content and hematocrit level were increased by this same maneuver. Contraction of the spleen was responsible for the increased oxygen content.

OPPENHEIMER

Friedman, E. W., Davidoff, D., and Fine, J.: Hypothermia in Hemorrhagic Shock. Am. J. Physiol. **185:** 521 (June), 1956.

Dogs were more tolerant to the hypotension of hemorrhage if precooled to 28 C. Survival time after transfusion was also prolonged. However, precooling did not prevent death. Addition of an antibiotic to transfusion provided for survival. In normothermic dogs an antibiotic did not produce recovery from hemorrhagic shock. Precooling sustained antibacterial defense mechanism, which was lost in a normothermic animal. Cooling was not effective if used after hemorrhagic shock had been produced. Rapid transfusion was well tolerated in normothermic dogs in hemorrhagic shock but precipitated ventricular fibrillation if the dogs were cooled and shocked.

OPPENHEIMER

Johnstone, F. R. C.: Measurement of Splanchnic Blood Volume in Dogs. Am. J. Physiol. **185:** 450 (June), 1956.

Splanchnic blood volume was measured using P^{32}-labeled erythrocytes. The animals were eviscerated. Splanchnic blood volume was 21.7 per cent of circulating blood volume and 17.7 ml. per Kg. of body weight.

OPPENHEIMER

Burton, A. C. and Rosenberg, E.: Effects of Raised Venous Pressure in the Circulation of the Isolated Perfused Rabbit Ear. Am. J. Physiol. **185:** 465 (June), 1956.

In most cases flow through the isolated perfused ur increased as the hydrostatic pressure was ele- ated. This was due to passive distention of the essels. Nevertheless, in 6 of 37 cases, there was a ll in inflow and outflow when the hydrostatic pres- ure was highest. Interpretation was difficult because utflow fell below inflow as hydrostatic pressure was ised. This suggests an increase in capillary filtra- ion. The authors suggest that a veno-vasomotor eflex may have raised venous pressure in somewhat ess than half the cases. Data obtained do not eparate reflex from possible myogenic effects. It an occur without connection to the central nervous ystem.

OPPENHEIMER

Rosenberg, E.: Local Character of the Veno-Vasomotor Reflex. Am. J. Physiol. **185:** 471 (June) 1956.

The author used critical closing pressure to measure vasomotor tone in rabbit legs. When venous pressure was increased there were elevations in critical closing pressure in 7 out of 8 cases. These changes were independent of nervous connections. The observed results are ascribed to a local veno-vasomotor reflex.

OPPENHEIMER

Brown, F. K.: Cardiovascular Effects of Acutely Raised Intracranial Pressure. Am. J. Physiol. **185:** 510 (June), 1956.

The most prominent factor in the response to increased cerebrospinal fluid pressure was observed to be vasoconstriction. The effects were primarily neurogenic. The venomotor system was also actively contracted.

OPPENHEIMER

Nylin, G., Blomer, H., Jones, H., Hedlund, S., and Rylander, C.: Further Studies on the Cerebral Blood Flow Estimated with Thorium-B-Labeled Erythrocytes. Brit. Heart J. **18:** 385 (May), 1956.

Thorium-B-Labeled erythrocytes were injected into the internal carotid artery of 11 persons and into an arm vein of 18 others. Blood samples were removed simultaneously from both jugular bulbs in 7 of the first group and 6 of the second. Blood samples were removed simultaneously from 1 brachial artery and 1 jugular bulb in the other 12 persons in the second group.

Parallel curves from both jugular bulbs suggest complete cerebral mixing. Differences may be due to local disease.

The mean cerebral blood flow was 0.84 per cent or 12 per cent of the cardiac output; the cerebral pool volume 77 per cent or 2 per cent of the total blood volume; and the turn over of blood in the brain 11.2 per minute.

SOLOFF

Pliper, J., Lochner, W., and Schürmeyer, E.: Comparative Determinations of the Heart Output according to Fick's Principle with Oxygen and with P-Amino-Hippuric Acid. Arch. Kreislaufforsch. **23:** 177 (Dec.), 1955.

In 11 dogs the average deviation of the heart output, determined from the oxygen consumption and concentrations, from that determined by constant velocity infusion of p-amino-hippuric acid into the pulmonary artery through a catheter with determination of the concentration in femoral artery blood, was ±16 per cent. The advantages of the infusion method are that determination of oxygen consumption is not necessary, the results are independent of changes in respiration, and rapid changes in cardiac output can be recognized. The disadvantages are that the determination of the p-amino-hippuric acid is less exact than that of oxygen, and that the former method cannot be used when the renal blood flow is abnormally low.

LEPESCHKIN

Huang, K.-C., and Bondurant, J. H.: Effect of Total Body-X-Irradiation on Plasma Volume, Red Cell Volume, Blood Volume and Thiocyanate Space in Normal and Splenectomized Rats. Am. J. Physiol. **185:** 446 (June), 1956.

Normal rats, irradiated with a single dose of 600 r, were observed to have a decrease in plasma volume during the first 8 days. However, by the tenth day an increase was noted. After irradiation the reduction in red cell volume and hematocrit value developed gradually. By the tenth day these changes were marked. Changes in thiocyanate space were phasic. There was an increase on the fourth day followed by a decrease. Nevertheless, it was again elevated on the tenth day after irradiation. Splenectomized rats showed similar changes in thiocyanate space. Blood volume changes were variable. In these splenectomized subjects red cell volume was very low, but plasma volume was increased. These changes were present 4 days after exposure to x-ray.

OPPENHEIMER

Patterson, G. C.: The Role of Intravascular Pressure in the Causation of Reactive Hyperaemia in the Human Forearm. Clin. Sc. **15:** 17, 1956.

The author attempted to determine whether the vasodilatation following circulatory arrest could be abolished or modified by elevation of the pressure in the vessels during the period of arterial occlusion. The pressure was raised by sucking blood into the arm and trapping it there. The study was performed on 8 healthy men, in whom both forearms were placed in plethysmographs. The circulation in each case was arrested for 5 minutes. One forearm was packed with blood by applying to it suction equivalent to 100 mm. Hg below atmospheric pressure.

The results indicated that by increasing the quan-

tity of blood in the forearm during arrest of the circulation, the following reactive hyperemia was greatly diminished in extent, although the flow 5 seconds after release was often little altered.

It was concluded that the evidence supports a physical rather than a chemical hypothesis as the basis for the increased blood flow during reactive hyperemia.

ABRAMSON

Sawyer, C. H., and Gernandt, B. E.: Effects of Intracarotid and Intraventricular Injections of Hypertonic Solutions on Electrical Activity of the Rabbit Brain. Am. J. Physiol. **185:** 209 (Apr.), 1956.

Hypertonic intracarotid injections of saline or glucose produced electroencephalographic changes in the telencephalon and the diencephalon. These changes lasted 20 seconds. The solutions had no action if injected into the external carotid artery. The 2 substances injected are known to cause release of antidiuretic hormone. In the ventricle hypertonic saline caused seizures but no electroencephalographic changes. Repeated intracarotid injections of hypertonic saline caused seizures localized to hippocampus and amygdala in more than half of the cases.

OPPENHEIMER

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Platts, M. M., and Hanley, T.: The Effects of the Carbonic Anhydrase Inhibitor Acetazoleamide on Chronic Respiratory Acidosis. Acta med. scandinav. **154:** 53 (fasc. 1), 1956. Abstracted, Circulation **15:** 756 (May), 1957.

Sievers, M. L., and Vander, J. B.: Toxic Effects of Ammonium Chloride in Cardiac, Renal and Hepatic Disease. J.A.M.A. **161:** 410 (June 2), 1956.

In 4 patients a toxic condition was produced by ammonium chloride. The useful function of this drug in preventing a hypochloremic acidosis and poor diuretic response to mercurials is not minimized. It is stressed that ammonium chloride may induce severe toxic conditions, particularly in the presence of renal or hepatic disease. With impairment of kidney function progressive hyperchloremic acidosis may occur and in the presence of liver disease a state similar to spontaneous hepatic coma may be produced. During treatment with ammonium chloride, periodic electrolyte determinations are indicated. In the treatment of reactions to this drug, ammonium chloride should be discontinued and acidosis may then be combatted with sodium salts, but no specific therapy is known that will influence the recovery from hepatic coma.

KITCHELL

Heidorn, G. H.: The Effect of Corticotrophin (ACTH) on Ammonia Production in the Nephrotic Syndrome. Am. J. M. Sc. **631:** 644 (June), 1956.

ACTH was administered to 10 patients with nephrotic syndrome ranging in age from 4 to 28. Eight patients responded well to this treatment; 2 died in uremia shortly after the recorded period. Urine ammonia excretion rose from 62 per cent to 380 per cent above the control levels in the 8 improved patients during administration of ACTH. Measurement of sodium ion excretion and urinary pH values during treatment could not be correlated with tubular ammonium ion formation. It may be assumed that ACTH has an effect upon enzyme systems in the tubular cells involved in the production of ammonia from amino acids. A less likely possibility is that increased amounts of glutamine are made available to this system for ammonia production.

SHUMAN

Young, J. V., and Daugherty, G. Y.: Use of the Artificial Kidney in the Production and Study of Experimental Hypokalemia. Proc. Staff Meet., Mayo Clin. **31:** 357 (June), 1956.

By means of the Skeggs-Leonards hemodialyzer, acute potassium depletion and hypokalemia were produced in 16 dogs and 6 pigs. The concentration of potassium in the plasma fell rapidly during the first 2 hours of dialysis to a minimal value of approximately 1.6 mEq. per liter. Although potassium continued to be removed at a relatively constant rate for as long as 5 hours, the concentration in blood plasma did not decrease further.

The changes in the electrocardiogram of the dog consisted of increase in the amplitude and width of the P wave, increase in the P-R interval, increase in the duration of the QRS complex and Q-T interval, widening and rounding of the T wave, and depression of the S-T segment. All these changes were best correlated in the electrocardiogram of the dog with the concentration of potassium in the plasma with the exception of depression of the S-T segment, which seemed to be more closely related to the quantity of potassium removed.

SIMON

Hawthorne, E. W., Brownlee, G. V. and Jason, R. S.: Development of Acute Pulmonary Edema and Death in Dogs with Aortic Insufficiency Following Renal Artery Constriction. Am. J. Physiol. **185:** 474 (June), 1956.

Dogs, which had experimental aortic insufficiency, died within 2 days when subjected to renal artery constriction. Acute massive pulmonary edema and congestion were found at necropsy.

OPPENHEIMER

Mavor, G. E., Harder, R. A., McEvoy, R. K., McCoord, A. B., and Mahoney, E. B.: Potassium and the Hypothermic Heart. Am. J. Physiol. **185:** 515 (June), 1956.

Plasma potassium fell with surface cooling to 26 C. Respiratory control prevented any excess of carbon

dioxide. Glucose showed changes similar to those observed for potassium. This fall in plasma glucose may be due to faulty utilization during the hypothermia. There was negative potassium arteriovenous difference in the coronary circulation during caval occlusion and circulatory standstill.

OPPENHEIMER

Hawthorne, E. W., Brownlee, G. V., and Spellman, M. W.: Prophylaxis against Acute Pulmonary Edema and Death in Dogs with Aortic Insufficiency Following Renal Artery Constriction Afforded by Prior Construction of an Atrial Septal Defect. Am. J. Physiol. **185:** 479 (June), 1956.

The test objects were dogs with interatrial septal defect and aortic insufficiency. Renal artery constriction does not result in death of these dogs as it does in those with aortic insufficiency alone. However, renal artery constriction does produce congestive failure.

OPPENHEIMER

RHEUMATIC FEVER

Stollerman, G. H.: Rheumatic Fever. Arch. Int. Med. **98:** 211 (Aug.), 1956.

In the absence of a specific cure for rheumatic fever, there are many therapeutic measures that reduce the severity of the acute attack and improve the patient's chances for recovery and longevity. Prompt eradication of Group A streptococci and continuous prophylaxis against subsequent infection with this organism is perhaps the most important single measure. Also helpful, however, is adequate suppression of the inflammatory process with either salicylates, the adrenal cortical hormones, or both. The least such therapy does is to improve the patient's general condition and reduce the toxic manifestations of the disease that can be harmful and dangerous to the patient with severe carditis. The evidence for a modifying effect of the antirheumatic agents upon ultimate cardiac damage is equivocal but suggestive.

The proper control of side effects of treatment, careful treatment of heart failure with digitalis and diuretics, and the management of the patient's activity are all important supportive measures. Under such management the prognosis for the patient with acute rheumatic fever has been improving steadily.

BERNSTEIN

Karp-Giora, S.: The Prognosis of Rheumatic Fever in Relation to Severity of Carditis. Bull. St. Francis Hosp. & Sanatorium **13:** 19 (Jan.–Apr.), 1956.

Eighty-four rheumatic boys and girls were studied to evaluate factors that may be associated with progressive rheumatic heart disease. Forty children showed definite but mild progressive cardiac damage at the end of the period of observation. In these rheumatic activity was considered as mild or subclinical at the beginning of the observation period. Forty-four children showed progressive heart disease of various degrees, from moderate to severe. In these, active carditis was known to exist at the time that the period of observation began. In most of these rheumatic activity was still present after a period of observation of an average 5.2 years. The dominant factors associated with progressive heart disease are the existence of active carditis and its duration and severity.

This study further substantiates the observation that one of the most sensitive indices for the existence of active carditis is the prolongation of the QTc on the electrocardiogram. Those in whom the QTc remained prolonged almost without exception showed progressive heart disease.

HARRIS

Lieber, S. L., and Holoubek, J. E.: Acute Rheumatic Fever in a Large Southern Hospital over the Five Year Period 1950 through 1954. Ann. Int. Med. **45:** 7 (July), 1956.

At the Confederate Memorial Medical Center, in Shreveport, Louisiana, a 1,000 bed general hospital for indigent patients, admissions to the Departments of Internal Medicine and Pediatrics between the years 1950 and 1954 were analysed with particular reference to the incidence of rheumatic fever. The total number of admissions during this period was 27,522. The diagnosis of acute rheumatic fever was established in 162 cases (0.59 per cent). The incidence of rheumatic fever was 1 case among 170 admissions. This is comparable to the incidence found during the same period at the Charity Hospital of New Orleans. During the period from 1910 to 1925 the proportion of cases of rheumatic fever at the Charity Hospital in New Orleans was 1:161 and at the Massachusetts General Hospital in Boston it was 1:170. The total of 162 cases diagnosed as acute rheumatic fever included 20 white patients and 142 Negro patients. The high incidence of the disease in Negro patients can be attributed to the low economic level of this portion of the population with resultant increase in incidence of and exposure to infections resulting from Group A streptococci. The total series included 65 males and 97 females. The ages ranged from 3 to 39 years. The median age was 14 years. In 92 patients the infection was the initial attack, and in 70 it represented a recurrence of rheumatic fever. The disease occurred most frequently in March and November. Of the 9 patients who died in this series, 8 were Negroes and 1 was white. All the deaths resulted from intractable cardiac failure. Dividing the manifestations into groups, it was found that arthritis was the major manifestation in 63.6 per cent, carditis in 56.2 per cent, chorea in 9.3 per cent, subcutaneous nodules in 3.1 per cent, and erythema marginatum in 0.6 per cent.

WENDKOS

Adams, F. H.: An Appraisal of Certain Acute Phase Reactants in a Single Blood Sample and Their Value in the Diagnosis of Acute Rheumatic Fever. J. Pediat. **49:** 16 (July), 1956.

Upon a single sample of serum obtained from 128 children in the acute phases of many different disease states (acute rheumatic fever, disseminated lupus, acute nephritis, streptococcal disease of the throat, respiratory disease of unknown cause, rheumatoid arthritis, asthma and obesity) 4 different determinations were made. These were: mucoprotein-tyrosine, antistreptolysin O titer, C-reactive protein, and nonglucosamine polysaccharides. Statistical studies were done on the results obtained. It was concluded that no single determination correlated well with the presence of acute rheumatic fever but of these tests when considered together the mucoprotein-tyrosine, and antistreptolysin O titer were suggestive. The authors believe that these 2 tests may help in distinguishing mild acute rheumatic fever from acute rheumatoid arthritis.

HARVEY

Selman, D., and Halpern, A.: Pitfalls in the Determination of C-Reactive Protein, an Acute-Phase Reactant. Angiology **7:** 292 (June), 1956.

Detailed directions are provided for determination of the presence of C-reactive protein. Interpretation of the test is discussed and the clinical applicability of the procedure is illustrated by case reports.

WESSLER

ROENTGENOLOGY

Saltz, N. J., Luttwak, E. M., Schwartz, A., and Goldberg, G. M.: Danger of Aortography in the Localization of Pheochromocytoma. Ann. Surg. **144:** 118 (July), 1956.

The authors presented a case report in which the use of aortography to demonstrate the presence of a cortical tumor of the adrenal gland resulted in death. A 16-cm. 18-gauge needle was inserted into the abdominal aorta without difficulty and 70 per cent Diodrast was injected into the lumen. Excellent visualization of the tumor was obtained. However, about 1 hour after being returned to her bed, the patient became nauseated and vomited, and the blood pressure rose to 210/150 mm. Hg. Regitine was given intravenously, and the blood pressure fell to a low level and then slowly rose. Eleven hours following aortography the patient went into shock, which did not respond to treatment, and died 13 hours later. Autopsy revealed an intracapsular hemorrhage in a pheochromocytoma of the right adrenal gland.

It was believed that the patient experienced a hypertensive crisis resulting from the pouring out of large amounts of epinephrine followed by the development of shock. It was also thought that the initiating cause of the hemorrhage around the tumor was related to the aortography and that this change in the tumor was responsible for the epinephrine response.

The authors concluded that the use of aortography in localization of a pheochromocytoma was highly questionable.

ABRAMSON

Rollins, M. and Bonte, F. J.: The Cardio-Thoracic Ratio in Roentgenography of the Normal Pregnant Patient. Am. J. Roentgenol. **76:** 64 (July), 1956.

A study of the cardiothoracic ratio during pregnancy and the postpartum period in 69 patients without cardiovascular disease revealed that only 1 patient had a ratio of over 55 per cent. There was a trend in the series toward increase in the transverse diameter of the heart, accompanied by a corresponding increase in the internal diameter of the thorax in most cases.

SCHWEDEL

Bolt, W., Michel, D., Schulte, W., Valentin, H. and Venrath, H.: Angiographic Studies During the Forced Expiration Test of Bürger. Ztschr. Kreislaufforsch. **45:** 402 (June), 1956.

In 6 normal volunteers angiographic study showed that during forced expiration (Valsalva experiment) blood flow into the thorax from the arms ceases completely while inflow from the abdomen continues, and is slowed only in some persons. Selective angiography of the pulmonary vessels by means of dye injection through a catheter in a pulmonary vein showed that during the experiment the blood flow is as rapid as during respiratory standstill alone; this proves that increased intrathoracic pressure does not cause increased resistance to pulmonary blood flow and accordingly does not overload the right ventricle. The prolonged phase of capillary filling that was found under these conditions indicates rather a dilatation of the capillaries.

LEPESCHKIN

Actis-Dato, A., Angelino, P. F., and Brusca, A.: An Angiopulmographic study of the Lesser Circulation in Mitral Stenosis. Am. Heart J. **52:** 1 (July), 1956.

This report deals with the angiopulmonic aspects of the lesser circulation in 500 patients with mitral stenosis, of whom 250 underwent mitral commissurotomy. Cardiac catheterization was carried out in 50 patients of the total group. On angiographic examination, there was found a more or less marked enlargement of the main trunk in all instances; likewise, the left and right pulmonary arteries were also usually larger than normal. However, changes in the medium-sized and small pulmonic vessels were of different degrees. The main pulmonary veins were larger than normal and during the passage of the dye through the veins, the lungs show a coarse dotting and irregular striae. In the normal

patients 4 seconds after the injection of the dye in the cubital vein, the pulmonary artery and its branches are completely emptied. In patients with mitral stenosis, after 6 or 8 seconds, the dye is still present in the pulmonary artery. Where passage of the dye is only slightly delayed, the clinical complaint is usually only dyspnea on exertion. Where passage of the contrast medium is more markedly slowed, dyspnea is usually severe and acute pulmonary edema may occur. Hemoptysis may be present. In most of these latter cases, the pulmonary artery pressure is elevated to a variable degree as well as capillary pressure and pulmonary vascular and total resistances.

RINZLER

SURGERY AND CARDIOVASCULAR DISEASE

Staubesand, J., and Andres, K. H.: Observations on Severed Arteries. A Contribution to the Physiology of Spontaneous Hemostasis. Arch. Kreislaufforsch. **23:** 242 (Dec.), 1955.

If muscular arteries are cut, contraction of the muscle cells in the arterial wall causes invagination of the end into the lumen of the artery; this contributes to spontaneous hemostasis. This invagination depends upon a mechanical stimulus of sufficient strength. No invagination occurs if the artery is cut with a very sharp knife, if the artery was previously contracted, or when contraction is inhibited by inflammatory processes or arteriosclerosis. Mechanical stimuli not leading to gross injury may also lead to invagination of the muscular layers. Slight invagination may occur also when dead arteries are cut; in this case it is due to retraction of the elastic elements in the arterial wall. Some of the previously described intravascular nodules or funnels, which have been interpreted as having a physiologic function, may have been invaginations appearing during or after death.

LEPESCHKIN

Humphries, A. W., deWolfe, V. G., and LeFevre, F. A.: Analysis of One Hundred Twenty Consecutive Cases of Major Arterial Grafts. J.A.M.A. **161:** 953 (July 7), 1956.

Of 120 arterial grafts, 90 have been completely successful and 30 have resulted in some complications. Of these 30, 12 patients died. The most important single thing in the preoperative study was angiography. The contraindication to selective grafting is shown in the angiogram by an inadequate outflow. When the blood delivered at the proximal end of the graft cannot be drained off by adequate vessels distal to the graft, thrombosis is likely. Of those individuals with favorable preoperative angiographic findings, there was a 96 per cent chance that the graft initially would be successful. If the occlusion is aortic there is approximately a 95 per cent chance the graft will remain satisfactory; and if the occlusion is femoral there is a 90 per cent chance it will remain satisfactory. When angiography shows that outflow is not satisfactory the chances of successful graft are reduced to 24 per cent. It is noted that among the patients whose grafts are failures, none required amputation of a limb and several experienced definite symptomatic improvement.

KITCHELL

Poppe, J. K.: New Vascular Clamp Without Handles for Lateral Resection of Aortic Aneurysms. J.A.M.A. **161:** 968 (July 7), 1956.

A new clamp for application across the neck of aortic aneurysms is described. The jaws are 160 mm. in length. Both ends are held together by bolts with winged nuts so that adjustment may be made for both the thickness of the aneurysm neck and the tension to be applied.

KITCHELL

Wachtel, F. W., Ravitch, M. M., and Grishman, A.: The Relation of Pectus Excavatum to Heart Disease. Am. Heart J. **52:** 121 (July), 1956.

The authors report on 13 patients with this illness studied since 1952, of whom 11 were operated upon. A review of the literature is given. The symptomatology included dyspnea on exertion, occasionally palpitation, and also occasionally regurgitation. The radiographs showed cardiac displacement. Seven patients had systolic murmurs ranging in intensity from grades 1 to 3, best heard along the sternal border. The electrocardiogram and vectorcardiographic findings are the result of cardia rotation. The operation used consisted in subperichondral resection of all deformed costal cartilages from their junction with the sternum to the lateral limit of the deformity. From 4 to 6 cartilages are usually involved on each side. The xiphisternal junction is divided and the intercostal bundles divided from the sternum. This operative procedure can satisfactorily correct the deformity of pectus excavatum with good physiologic and cosmetic results.

RINZLER

Farrar, T., Adson, M. A., Kirklin, J. W., Martin, W. J., and Barker, N. W.: Surgical Treatment of Acute Rupture of Abdominal Aortic Aneurysms: Report of Two Cases. Proc. Staff Meet., Mayo Clin. **31:** 299 (May 16), 1956.

It is shown that resection of a diseased segment of aorta and replacement with an aortic homograft or a suitable prosthesis is anatomically possible in most patients who have arteriosclerotic aneurysms of the abdominal aorta. Successful application of this procedure in the emergency presented by acute rupture of an aneurysm is reported. As would be expected, the mortality rates and the loss of limbs in such a group of patients are greater than they are in those having elective operations. However, since

the future of untreated patients is hopeless, emergency resection and grafting for acute rupture of an abdominal aortic aneurysm are justified.

SIMON

Petersen, O.: Rib Notching Following the Blalock-Taussig Operations. Acta Radiol. **45:** 308 (April), 1956.

Rib notching may occur in conditions other than coarctation of the aorta: cavernous hemangioma of the thoracic wall; arteriovenous aneurysms of intercostal vessels; neurofibromatoses; tuberous sclerosis; in certain instances of hypertensive and arteriosclerotic and aortic valvular disease, dilatation of the intercostal veins; and tetralogy of Fallot. In recent years several articles have stressed the occurrence of rib notching several months after the Blalock type of anastomosis had become thrombosed.

The author surveyed his own material to determine the validity of the association between rib notching and anastomotic closure. Seventeen of 100 operative cases disclosed characteristic rib notching not evident prior to the anastomosis. Three of the 17 were closed, while the other 14 remained patent by the usual criteria of persistence of the arteriopulmonary systolic and diastolic murmurs. In 5 instances angiocardiography demonstrated increased pulmonary blood flow.

SCHWEDEL

Campbell, G. S., Crisp, N. W., and Brown, E. B., Jr.: Total Cardiac By-Pass in Humans Utilizing a Pump and Heterologous Lung Oxygenator (Dog Lungs). Surgery **40:** 364 (Aug.), 1956.

Maintenance of respiratory function with isolated mammalian lungs has been reported from experimental laboratories since the nineteenth century. Recently several investigators successfully employed homologous lungs and various blood-pumping mechanisms during cardiac by-pass in dogs, but lungs of various species perfused with heterologous blood developed acute congestion with massive pulmonary edema. In this study human blood was perfused through isolated heterologous lungs (dog lungs) without the development of pulmonary edema; and the edema was prevented by: (a) dextran perfusion to removed heparinized dog blood, (b) open noncannulated pulmonary veins, (c) depulsated pulmonary artery, (d) care as to ventilation of the isolated heterologous lung. Whereas the dog lungs in vivo will tolerate a blood flow of several liters per minute at a normal pulmonary artery pressure, the isolated lungs of the dog will accept a flow of only 400 to 800 ml. of either autologous blood, homologous blood, or heterologous (human) blood at the same pulmonary artery pressure; greater flows producing pulmonary edema. It was noted that glass seems to have a detrimental effect on the blood clotting mechanism as evidenced by the fact that in earlier laboratory experiments with a partial glass circuit all the dogs bled to death postoperatively, whereas with an all plastic system none showed any hemorrhagic tendency.

Seven patients had been subjected to intracardiac surgery while their cardiorespiratory function was maintained via the pump-biologic oxygenator described in this study. These patients weighed from 15 to 58 Kg., the by-pass flows varied from 350 to 1,000 ml. per minute, and the duration of the cardiac by-pass was from 15 to 49 minutes. One patient (a 55-Kg. man with traumatic interventricular septal defects) is the only long-term survivor and another patient (a 46-Kg. woman with tetralogy of Fallot) died on the fourth postoperative day with outflow obstruction of the right ventricle. The remaining 5 patients died either at surgery or within several hours postoperatively. The intracardiac procedures in these 5 subjects were (1) attempted correction of mitral insufficiency; (2) closure of interatrial and interventricular septal defects in a patient with corrected transposition of the great vessels; (3) excision of left ventricular aneurysm; (4) persistent interventricular defect following attempted correction of tetralogy of Fallot; (5) right ventricular failure following closure of a ventricular septal defect in a patient with severe pulmonary hypertension. Bleeding and clotting times were normal at the end of the by-pass and platelet counts ranged from 92,000 to 166,000.

MAXWELL

Lillehei, C. W., DeWall, R. A., Gott, V. L., and Varco, R. L.: The Direct Vision Correction of Calcific Aortic Stenosis by Means of a Pump-Oxygenator and Retrograde Coronary Sinus Perfusion. Dis. Chest. **30:** 123 (Aug.), 1956.

Blind or closed technics for the correction of calcific aortic stenosis through either the left ventricle or the aorta have been encouraging but not altogether satisfactory. The failures or deaths have been from uncontrollable hemorrhage, ventricular fibrillation, or the creation of aortic insufficiency. The successes have all too frequently been partial and incomplete. A direct vision approach to the aortic valve utilizing the pump-oxygenator would lessen or obviate many of these complications. The obstacles to this approach (interruption of the coronary artery circulation, coronary air embolism) can be prevented by a retrograde perfusion of oxygenated blood into the coronary sinus.

In a severely incapacitated 37-year-old woman this technic was applied to the correction of calcific aortic stenosis. Total cardiopulmonary by-pass was instituted utilizing a pump and a simple disposable oxygenator. The aortic valve was exposed for 14 minutes through the opened aorta. This valve was severely stenotic and had a fishmouth orifice of no more than 4 mm. The commissures were opened to the annulus with dissecting scissors. Some of the verrucous calcium was also trimmed off and the

ynechia binding the cusps against the inner aortic vall were cut with the scissors tip. These procedures esulted in a valve appearing to function very atisfactorily despite its diseased state. During this nterval the myocardium was maintained by the etrograde coronary sinus perfusion of a small uantity of oxygenated blood from the oxygenator. The heart remained a healthy pink color and continued to beat at a slow regular rhythm throughout his interval. Recovery was uncomplicated and the patient's status postoperatively has improved dramatically.

MAXWELL

Wilson, M. G.: "Stitch-Gun" for Suturing Atrial Septal Defects. Lancet **1:** 426 (April 14), 1956.

The author describes an instrument, held in the hand like a pistol, by means of which sutures can be placed in atrial defects, elsewhere in the heart, or in other parts of the body where visibility or room to maneuver is lacking.

McKUSICK

Horton, R. E.: Use of Grafts in Treatment of Atherosclerosis of Lower Limbs. Brit. M. J. **1:** 81 (Jan. 14), 1956.

In a series of 29 patients with atherosclerotic obstruction of the arteries of the lower limb grafting was performed. In distinction to the experience with grafting in more proximal arteries, a high incidence of thrombosis, both early and delayed, led the author to conclude that grafting by the end-to-end technic is not worthwhile beyond the proximal part of the femoral artery. End-to-side grafts may prove more successful.

McKUSICK

Muller, W. H., Jr., and Dammann, J. F.: Results Following the Creation of Pulmonary Artery Stenosis. Ann. Surg. **143:** 816 (June), 1956.

In patients with congenital heart disease who have a large communication between the 2 sides of the heart as in the case of a large ventricular septal defect or single ventricle, pulmonary hypertension occurs usually with excessive pulmonary blood flow. A procedure of creating pulmonary stenosis was developed in order to place the point of high resistance in the outflow tract of the pulmonary circulation rather than in the small pulmonary arteries to prevent progressive changes of medial hypertrophy and intimal fibrosis in these vessels. It has been used in 25 patients, a total of 28 times, during the past 4½ years. There were 9 operative deaths and 1 late death in these patients. In 15 surviving patients, the results have been classified as excellent in 11 patients, good in 3 patients and poor in 1. The procedure is a palliative one and should be used only in those patients in whom an open cardiac procedure with definitive repair of the intracardiac defect cannot be effected.

MAXWELL

Brown, I. W., Jr., Hewitt, W. C., Jr., Young, G., Sealy, W. C., and Harris, J. S.: A Simple, Expendable Blood Oxygen-Gas Exchanger for Use in Open Cardiac Surgery. Surgery **40:** 100 (July), 1956.

A simple, expendable, plastic blood oxygenator for use in extracorporeal circulation has been described. Experimental studies in dogs and observations made in 1 patient perfused during cardiac surgery for over 2 hours have revealed efficient blood-gas exchange, normal post-perfusion red-cell survival, red-cell osmotic fragility, and low plasma hemoglobin levels. Plasma fibrinogen levels determined before and after use of the oxygenator have remained normal. A reduction of approximately 50 per cent in the platelet count has been observed.

In addition, the bag-oxygenator described is designed to collect and rapidly oxygenate venous blood directly from a blood donor. In this respect it may be used in other instances when the transfusion of oxygenated blood might be desirable. Other advantages and limitations are discussed.

MAXWELL

Silen, W., Mawdsley, D. L., Miller, E. R., and McCorkle, H. J.: The Experimental Production of a Competent Aortic Valve. Surgery **40:** 78 (July) 1956.

A valve was constructed in the descending aorta of dogs by intussusception of a segment of the wall of the aorta. This valve allowed only minimal regurgitation, as demonstrated by cineroentgenograms. Comparative femoral and carotid pressure tracings, in a dog with experimentally produced aortic insufficiency in which a valvuloplasty was also done, showed that the valve significantly reduced the elevated pulse pressure of aortic insufficiency.

MAXWELL

Glenn, W. W. L., Gentsch, T. O., Hume, M., and Guilfoil, P. H.: The Surgical Treatment of Mitral Insufficiency with Particular Reference to the Application of a Vertically Suspended Graft. Surgery **40:** 59 (July), 1956.

Further experiments on the use of the left heart, transchamber, vertically suspended, cylindrical graft in the control of mitral insufficiency are described. Particular reference is made to the use of a prosthesis from a compressed Ivalon sponge. A comparison was made between the uncovered sponge and the sponge covered with tissue. In this regard, the sponge covered with inverted autogenous vein appeared to be superior at all stages of animal survival to either the plain sponge or the sponge covered with autogenous pericardium or homologous vein. The search is being continued in the laboratory for the ideal tissue coverage for the graft. Further experiments are anticipated on the use of a small segment of autogenous artery or vein placed at the point of contact of the prosthesis with the valve.

The results of the application of this technic to 3

patients severely incapacitated with mitral insufficiency are described. One patient had no improvement and the other 2 had equivocal improvement. It is thought by the authors that with a larger graft and with better graft coverage, and with relaxation of the graft and care in placing the graft directly in the regurgitant stream, better control of the insufficiency will result. Caution is advised in the further application of this technic to patients until more satisfactory methods are developed for coverage of a sponge sufficiently large to compensate the area of regurgitation.

MAXWELL

McAllister, F. F., and Fitzpatrick, H. F.: Constriction of the Mitral Annulus in the Correction of Certain Types of Mitral Insufficiency and as an Aid in By-Passing the Left Ventricle. Surgery **40:** 54 (July), 1956.

A technic is presented for producing annular constriction of the mitral ring. The fate of the suture has been followed for as long as 4 months and is still under study. Constriction of the mitral ring has been employed in 20 dogs as a means of trapping blood in the left atrium whence it could be withdrawn and pumped into the arterial system, thus by-passing the left ventricle. This technic permitted successful left ventriculotomy in 9 instances with survival. This same technic in combination with catheterization of the venae cavae and pulmonary artery has permitted total by-pass of the heart, using the animal's own lungs as oxygenators. In 2 out of 5 experiments this permitted successful left ventriculotomy, but there was only 1 permanent survival.

MAXWELL

DeWall, R. A., Warden, H. E., Lillehei, C. W., and Varco, R. L.: A Prosthesis for the Palliation of Mitral Insufficiency. Dis. Chest **30:** 133 (Aug.), 1956.

During exploratory surgery on patients afflicted with mitral insufficiency, the observation has been made by the authors and others that the regurgitant jet could be effectively controlled by the surgeon's index finger with significant improvement in the action of the heart as long as the finger remained as an obturator in this area of valvular deficiency. If one could place a finger-like obturator through the incompetent area of a defective mitral valve such that it would properly fill the insufficient area, the lesion would be palliated provided that at least 2 square centimeters of functioning valve area remained.

A polyvinyl sponge was used experimentally to straddle the posterior commissure of the mitral valve in the dog. This material is relatively nonreactive when inserted into the blood stream and will contract and be shaped as the pressures of the mitral leaflets dictate and thus tend to fill any area of valve deficiency that is present. In 28 animals the prosthesis was allowed to remain in situ for periods up to 10 months; 1 remaining animal is still alive for observation over a longer period. It was noted that even a mild degree of acute traumatic mitral insufficiency was not tolerated well in the animals used for this study; and the high incidence of infection despite antibiotics after placement of the prosthesis was noteworthy.

Although the pathology of acute experimental traumatic mitral insufficiency cannot be compared with rheumatic mitral insufficiency in man, the clinical implication is that this technic may be used to reduce the quantity of regurgitation present in patients with significant degrees of mitral insufficiency.

MAXWELL

UNCOMMON FORMS OF HEART DISEASE

Kilbourne, E. D., Wilson, C. B., and Perrier, D.: The Induction of Gross Myocardial Lesions by a Coxsackie (Pleurodynia) Virus and Cortisone. J. Clin. Invest. **35:** 362 (April), 1956.

From a patient with epidemic pleurodynia, Group B Coxsackie virus was obtained and injected into cortisone-treated adult mice. Gross myocardial necrosis was observed. These results were not obtained when virus or cortisone was administered separately. Specific viral antiserum prevented the myocarditis if given concurrently. The authors suggest the possibility of the conversion of benign pleurodynia to a serious, or even fatal, disease by the stimulus of endogenous or exogenous corticosteroids.

WAIFE

Drye, J. C., Coe, W. S., and Stamer, J. P.: Heart Wounds—A Long-term Follow-up of Twenty Cases. Am. J. Surg. **91:** 597 (April), 1956.

A follow-up study, ranging from 3 to 20 years, was made on 20 patients who had sustained heart wounds. Twelve were found to be working, 7 had no symptoms and no evidence of heart disease. The remaining 5 did have definite complaints. Of the 8 patients who were not working, 4 had definite heart disease. No cases of constrictive pericarditis or false aneurysms were noted.

ABRAMSON

Haviar, V., Siska, K., and Klein, F.: A Successfully Operated Cardiac Tumor of Interesting Biological Structure. Cardiologia **29:** 132 (Fasc. 2), 1956.

A case is reported of a 37-year-old man without cardiac symptoms operated upon for a mixed tumor of the anterior wall of the left ventricle. The diagnosis was made preoperatively on the basis of the roentgenogram, which in the posteroanterior view showed a circumscribed prominence of the left ventricle and in tomograms suggested the presence of cystic and calcified areas in the protruding region. The electrocardiogram showed inversion of T in lead

I and remained unchanged over a long period of observation. At thoracotomy a cystic tumor of the left ventricular wall was found, which was emptied and drained. The patient had an uneventful recovery. On histologic examination the tumor tissue proved to correspond to a fibrolipomyoma with the myomatous portions apparently derived from blood vessels. The cystic portions of the tumor are regarded as lymphatic structures resembling a lymphoangioendothelioma.

PICK

Potts, R. E., and Williams, A. A.: Acute Myocardial Toxoplasmosis. Lancet **1:** 483 (April 21), 1956.

The authors report a fatal case of acute toxoplasmosis, with predominant myocardial involvement, occurring in a 30-year-old detective. Because of the widespread distribution of the causative organism in the animal kingdom it is possibly relevant that the patient's dog became ill with diarrhea and vomiting, remaining ill for 6 weeks, and finally died. (Enterocolitis is at times a manifestation of toxoplasmosis in dogs.) Beginning about the time of the dog's death, the patient developed malaise and persistent head cold. These symptoms were followed by cough productive of purulent sputum. The clinical manifestations, at the time of hospitalization were fever, pulse of 128, blood pressure of 85/60 mm. Hg, acute pulmonary edema, cardiomegaly, and left bundle-branch block. A diagnosis of Fiedler's myocarditis was made. Both the dye test and the complement-fixation test for toxoplasmosis were positive. Pyrimethamine and a sulfonamide were administered without benefit. The hospital course was characterized by mental confusion, intermittent diarrhea, enlargement of the liver, sacral edema, and in the last week before death a transient erythema of the trunk with a few petechiae.

Necropsy revealed chronic passive congestion and enlargement of the heart (weight 700 Gm.). Histologically there were inflammatory changes in the myocardium, particularly of the left ventricle. No toxoplasma organisms were seen in careful search of more than 100 sections. However, the organisms were isolated by injection of heart muscle into mice.

MCKUSICK

Chamberlain, J. M., Carberry, D. M., and Stefko, P. L.: Practical Aspects in the Management of Stab Wounds of the Heart. Am. J. Surg. **91:** 600 (April), 1956.

The management of patients with penetrating injuries to the heart is discussed. The cases are divided into 2 groups: those who die almost immediately and those who arrive at the hospital in various degrees of shock. The cause of death in the first group is usually due to destruction of significant branches of a main coronary artery or to large rents in the cardiac chambers or major vessels.

In those who reach the hospital, blood replacement is the first therapeutic approach, since this permits surgical exploration. According to the authors, the role of tamponade as a cause of death has been overemphasized, although it may be a contributing factor.

ABRAMSON

VALVULAR HEART DISEASE

Van der Hanvert, L. G., De Witte, P. E., and Joosens, J. V.: Septal Lines of Kerley. Incidence and Significance in Mitral Stenosis. Acta cardiol. **11:** 351 (Fasc. 4), 1956.

The hemodynamic findings in mitral stenosis were correlated with the occurrence of costophrenic septal lines of Kerley. There was a definite relationship between the presence of these lines and an increase in the pulmonary arterial wedge pressure above 20 mm Hg. A similar correlation could be established with narrowing of the mitral ostium to 1 cm or less. Contrariwise no relation was found between the occurrence of septal lines and the pulmonary arteriocapillary gradient or the pulmonary arterial resistance. Disappearance of these lines was usually noted after mitral commissurotomy. On this basis it would appear that the lines bear a relation to pulmonary venous hypertension but not to pressure elevations originating proximal to the pulmonary capillaries. They are probably due to dilated lymphatics and to thickening of the interlobar septa. The clinical value of this diagnostic sign lies in the possibility of estimating the degree of pulmonary venous hypertension and of following the evolution of mitral disease. In addition it may be helpful in the selection of patients for surgery especially in cases where cardiac catheterization is difficult or impossible.

PICK

Englert, M., and Denolin, H.: Pulmonary Ventilation Determined by the Helium Method in Mitral Stenosis. Acta Cardiol. **11:** 365 (Fasc. 4), 1956.

A study of pulmonary ventilation by the helium method in 31 cases of mitral stenosis revealed a moderate, absolute as well as relative, increase of the residual volume, which is in keeping with results obtained previously by other methods. In 13 patients a disturbance in intrapulmonary distribution of the inspired air could be demonstrated but it was not possible to establish a clear relationship of these alterations with hemodynamic findings. Such an inequality in air distribution might be dependent on structural changes caused by vascular congestion and probably is a factor in the etiology of dyspnea in mitral disease.

PICK

Spellman, M. W., and Balkissoon, B.: The Production and Evaluation of Ascites Secondary to Isolated Tricuspid Insufficiency in Dogs. Surgery **39:** 37 (Jan.), 1956.

The authors attempted to provide an experimental animal with sustained ascites secondary to a reproducible cardiac lesion, namely, tricuspid insufficiency. The valvular lesion was produced by the division of the chordae tendineae of the tricuspid valve. The results of the study on dogs demonstrated that isolated tricuspid insufficiency could be productive of ascites and cardiac edema provided the degree of valvular incompetence was severe enough.

ABRAMSON

Dresdale, D. T., Ripstein, C. B., Guzman, S. V., and Greene, M. A.: Postcardiotomy Syndrome in Patients with Rheumatic Heart Disease. Cortisone as a Prophylactic and Therapeutic Agent. Am. J. Med. **21:** 57 (July), 1956.

The postcardiotomy syndrome is characterized by the following clinical features, in descending order of frequency: fever, chest pain of a pleuropericardial nature, congestive heart failure, pleural effusion, polyarthritis, arrhythmia, abdominal pain, and subcutaneous nodules. A few instances of hemoptysis and psychosis have been reported. This syndrome was observed in 33 of 84 patients at variable intervals after mitral valvuloplasty. Cortisone had a definite suppressive effect on the syndrome. The incidence of postcardiotomy syndrome was 31 per cent in patients not receiving prophylactic cortisone and 7 per cent in the group receiving hormone prophylaxis. The immediate postoperative course of patients receiving prophylactic cortisone was less stormy than in those who did not receive cortisone. Therapeutically cortisone was superior to salicylates, pyramidon, and antibiotics, which did not affect the clinical manifestations of the postcardiotomy syndrome. Cortisone, varying from 50 to 300 mg. daily caused a dramatic remission of symptoms and fever in the postcardiotomy syndrome. It is recommended that ACTH be given prophylactically for 2 days preoperatively and for 8 to 10 days postoperatively to patients undergoing rheumatic mitral valvuloplasty.

HARRIS

Tweedy, P. S.: The Pathogenesis of Valvular Thickening in Rheumatic Heart Disease. Brit. Heart J. **18:** 173 (April), 1956.

The incidence and nature of surface deposits on rheumatic valves were interpreted by gross and microscopic study of 29 hearts with rheumatic mitral valve disease.

These studies indicate that thrombotic lesions appear commonly in the commissures on the contact line of the valve and on the extreme tip and less commonly elsewhere. These lesions change the contact line of the valve. The underlying histologic changes are interpreted as due to organizing or incompletely organized thrombotic deposits. The prevalent concept of fibrinoid degeneration is dismissed as superfluous.

Endothelial damage alone without inflammation can lead to thrombotic deposits that produce thickening of the valves and chordae and their fusions. The underlying histologic appearance depends upon the ages and degrees of organization of the thrombi.

SOLOFF

Bouvrain, Y., Fortin, P., and Pruvost, R.: The Effect of Mitral Commissurotomy on the General Condition. Arch. mal. coeur **49:** 97 (Feb.), 1956.

In 43 of 53 cases the average increase of weight after commissurotomy was 6.5 Kg. In 9 of the 36 women, premenstrual pelvic pains were present; these disappeared in all cases after the operation. In several patients subfebrile temperatures were observed without any other abnormal findings; these returned to normal after commissurotomy.

LEPESCHKIN

VASCULAR DISEASE

Sprofkin, B. E., and Blakey, H. H.: Acute Spontaneous Cerebral Vascular Accidents in Young Normotensive Adults. Arch. Int. Med. **98:** 617 (Nov.), 1956. Abstracted, Circulation **15:** 835 (June), 1957.

Drury, R. A. B.: Healed Dissecting Aneurysm of the Aorta. Brit. M. J. **2:** 1114 (Nov. 5), 1955.

Two patients are described in which long survival following dissecting aneurysm was probably due to 2 factors: location of intimal tear in the first portion of the descending aorta, and re-entry distally. The last was described in 1863 by Peacock as being responsible for an "imperfect natural cure." There was no proximal dissection; these were distal sheath-like dissections.

MCKUSICK

Woolling, K. R., and Shick, R. M.: Thrombophlebitis: A Possible Clue to Cryptic Malignant Lesions. Proc. Staff Meet., Mayo Clin. **31:** 227 (Apr.), 1956.

In 15 cases of unsuspected malignant disease, thrombophlebitis was the initial or principal symptom leading the patient to seek medical aid. The primary sites of cancer were as follows: pancreas in 3, ovary in 3, stomach in 2, lung in 1, breast in 1, probably prostate in 1 and indeterminate in 4. Clinical recognition of thrombophlebitis antedated the diagnosis of malignant disease by intervals of 4 days to 7 months; in 6 cases the interval was 3 or more months.

Greater suspicion of cancer in cases of apparently spontaneous thrombophlebitis among patients more than 40 years of age may stimulate earlier intensive investigation and diagnosis that may lead to more successful treatment in these cases. The mechanism of increased tendency toward thrombosis in this syndrome is unknown. The thrombosis, characteris-

tically, is relatively refractory to anticoagulant therapy.

SIMON

Baptista, L., Hoxter, G., Vellini, L., and Mungioli, R.: Electophoretic Studies in Disseminated and Fixed Lupus Erythematosus. Am. J. M. Sc. **232:** 83 (July), 1956.

The electrophoretic results obtained in 6 cases of disseminated and 12 cases of the fixed type of lupus erythematosus are presented. In the disseminated cases there was a general decrease of albumin and of beta globulin. In both forms of lupus there was an increase in α_2-globulin and in fibrinogen. An increase in γ-globulin was observed in 5 of the disseminated and 1 of the 12 fixed cases. Hyperproteinemia was noted in 1 of the disseminated and in 4 of the fixed cases. No correlation was established between the severity of the disease and the γ-globulin levels. It was found that in some cases there was a tendency toward normalization of the proteinemia with clinical improvement of the patients.

SHUMAN

Edwards, J. E., and Burchell, H. B.: Specimen Exhibiting the Essential Lesion in Aneurysm of the Aortic Sinus. Proc. Staff Meet., Mayo Clinic. **31:** 407 (July), 1956.

A specimen of heart with a noninfected aneurysm of an aortic sinus is described. The aneurysm in its basic nature was similar to each of 6 other noninfected aortic sinus aneurysms that the authors have observed. Sites of presentation and of rupture of these aneurysms depend on which of the 3 aortic sinuses is the site of origin and also more specifically on which part of the sinus is affected. Regardless of these details the basic lesion is a lack of continuity between the aortic media and the ring of the aortic valve. As judged from these observations on the pathology of the condition, surgical correction would require establishing continuity either directly or indirectly through a graft between these 2 structures.

SIMON

Wagner, F. B., Jr., Fried, P. H., and Perilstein, P. K.: Varicose Veins and Stasis Problems. The Industrial Physician's Interest and Potentialities. Indust. Med. & Surg. **25:** 337 (July), 1956.

The authors stress the importance of understanding the physiologic disturbances associated with the various types of venous disorders of the lower extremities so as to form a basis for individualization of treatment. They discuss the causes of primary varicosities, emphasizing the hereditary tendency and the constant stress of increased hydrostatic pressure, due to standing or to elevated intraabdominal pressure by straining. Complications of venous stasis are also enumerated. With regard to treatment, supportive therapy is discussed, such as the use of the Unna's paste boot and the elastic stocking.

According to the authors, varicosities secondary to deep thrombophlebitis should be treated by supportive procedures and not by deep venous ligation. Lumbar sympathectomy is not indicated.

Telangiectasia is a dilatation of capillaries and small venules, and cannot be considered to be a true varicosity. Many symptoms have been attributed to them but generally without basis. Surgery is contraindicated for this condition.

ABRAMSON

Storey, C. F., Nardi, G. L., and Sewell, W. H.: Traumatic Aneurysms of the Thoracic Aorta. Report of Two Cases, One Successfully Treated by Resection and Graft Replacement with the Aid of a Shunt. Ann. Surg. **144:** 69 (July), 1956.

The authors presented 2 cases of traumatic rupture of the thoracic aorta, one of which was successfully treated surgically. In each instance the rupture of the intima and media encompassed the entire circumference of the vessel.

The patient, who was treated with supportive therapy, had several bouts of circulatory collapse, but each time recovered with the use of whole blood transfusions. His status was satisfactory until 12 days after the accident, at which time, while drinking a glass of water, he developed a paroxysm of coughing followed by severe left chest pain, shock, and death. Postmortem examination revealed a circumferential laceration of the aorta just beyond the arch and immediately below the origin of the left subclavian artery.

The second patient was operated upon 4 years after he had sustained an injury to his chest. Except for occasional mild chest pain, he had been asymptomatic in the interval. At the time of operation an aneurysm of the thoracic aorta was found, which measured about 10 cm. in length and about 7 cm. in maximum diameter. An external shunt was made of 3 segments of freeze-dried pig aorta. The distal end was sutured end-to-end to the patient's subclavian artery and the other end to the normal aortic wall below the aneurysm. Then the aneurysm was resected, and aortic continuity was obtained by the use of a reconstructed freeze-dried homologous graft. Despite the fact that 24 hours were consumed in performing the operation, the postoperative course was uneventful.

ABRAMSON

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7–9170

APPLICATION DEADLINES SET FOR 1958 AHA RESEARCH SUPPORT

Applications for Established Investigatorships and Research Fellowships must be submitted to the Medical Director, American Heart Association, by September 15, 1957. Investigators who wish to apply for grants-in-aid must do so by November 1, 1957. Approved applicants will receive support for studies to be conducted during the fiscal year, beginning July 1, 1958.

Following are descriptions of the various categories:

RESEARCH FELLOWSHIPS: These are awarded to persons with doctoral degrees for periods of one or two years to enable them to train as investigators under experienced supervision. Annual stipends range from $3,800 to $5,700.

ADVANCED RESEARCH FELLOWSHIPS: These will be awarded for the first time next year, for periods of one or two years, to postdoctoral applicants who have had some research training and experience but who are not yet clearly qualified to conduct their own independent research. They will be permitted to spend up to 25 per cent of their time in professional and scientific activities not strictly of a research nature, provided that these will contribute to their professional development and do not involve services for a fee. Stipends for this new category will range from $4,600 to $6,500 annually. Research Fellowship application forms are to be used in making application for the advanced Research Fellowships. Classification as Research or Advanced Research Fellow is at the discretion of the Association's Research Committee.

ESTABLISHED INVESTIGATORSHIPS: These awards are given for periods up to five years, subject to annual review, in amounts ranging from $6,000 to $8,000, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. Applicants for Established Investigatorships may apply for grants-in-aid to support their research at the same time they apply for Established Investigatorships.

GRANTS-IN-AID are made to qualified investigators to provide support for specific projects.

For further information and application forms write to the Medical Director, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS

Early advance registration is urged for the American Heart Association's 33rd Annual Meeting and the 30th Scientific Sessions in Chicago, October 25–29. Registration and accommodation forms are now available from the Association.

The Scientific Sessions to be held at the Hotel Sherman, will commemorate the tercentenary of the death of William Harvey.

The subject of the George E. Brown Memorial Lecture to be given on Sunday morning, October 27, by Nelson W. Barker, M.D., Professor of Medicine, Mayo Foundation, is "The Current Evaluation of the Thrombosis Problem." Charles W. Rammelkamp, Jr., M.D., Professor of Medicine, Western Reserve University, will deliver the Lewis A. Conner Memorial Lecture on Saturday morning. His paper will deal with problems of rheumatic fever.

Preceding the regular Scientific Sessions will be an all-day scientific program on Friday, October 25 for physicians in general practice on the subject of "Prevention and Management of Cardiovascular Emergencies." This special course is open to all registrants at the Annual Meeting. On Friday evening, a special session on "Instrumental Methods in Cardiovascular Diagnosis" will be held.

The Saturday morning program will be devoted to a General Session which will feature, in addition to the Conner Memorial Lecture,

the presentation of the Albert Lasker Award of the American Heart Association. The Association's Council on Rheumatic Fever and Congenital Heart Disease will hold a luncheon on Saturday. The afternoon hours will be occupied with Special Sessions of the Sections on Clinical Cardiology and on Circulation, and of the Council on Rheumatic Fever and Congenital Heart Disease.

In addition to the Brown Memorial Lecture, a General Session has been scheduled for Sunday morning. The Community Service and Education Council will hold a luncheon on Sunday. The Council has also scheduled a Sunday afternoon session, jointly with the Staff Conference of Heart Associations, on "Community Service—Its Significance for Heart Associations." In addition, the Council will sponsor a Sunday afternoon scientific panel, to be organized by Dr. Herbert Pollack, Chairman of the Association's Nutrition Committee, on "The Present Status of Fat Metabolism and Atherosclerosis." Among the participants in the panel will be Herman Hilleboe, M.D., New York State Commissioner of Health, and Dr. Robert Eugene Olson, Professor of Biochemistry and Nutrition, Graduate School of Public Health, Pittsburgh.

The Association's Annual Dinner, including the presentation of Gold Heart awards, will be held Sunday evening. Scheduled for Monday morning are Special Sessions of the Sections on Basic Science and on Cardiovascular Surgery and of the Council for High Blood Pressure Research.

Six Assembly Panels will be in session on Monday. The annual general session of the Association's Assembly will meet on Tuesday morning to review panel recommendations and elect officers and board members of the Association.

ASSOCIATION ISSUES NEW MATERIALS

Among the new Heart Association materials of interest to physicians are the following:

"Heart Drawings," a new Heart Association portfolio which contains three large anatomical drawings in color, each on a separate page, of the normal heart and great blood vessels. In addition to the normal anterior and posterior views, a cross section in the coronary plane is presented. Anatomical structures are numbered and a key is provided. The drawings, which are designed for use by medical students, nurses and college physiology students, have been prepared by Leon Schlossberg, medical illustrator at Johns Hopkins University. The price of the portfolio is 50¢. The same drawings, in color slides, 3¼ x 4 inches or 2 x 2 inches, are priced at $15.00 and $3.00, respectively.

"How the Dentist Can Protect His Patients from Bacterial Endocarditis," a revision of a leaflet for dentists. It features a chart of treatment schedules based on Section IV of the 1956 revision of the AHA statement entitled "Prevention of Rheumatic Fever and Bacterial Endocarditis Through Control of Streptococcal Infections."

"High Blood Pressure," a 7-minute, 16 mm., color film produced for the Association by Churchill-Wexler. The film can be used for TV or direct audience viewing. This second in a series of three short films on aspects of cardiovascular disease provides an excellent visual aid to a physician addressing a group of lay people. The first film, recently issued, was "Coronary Heart Disease," the third, now in preparation, will deal with strokes.

A complete catalogue of American Heart Association materials for physicians, including publications, teaching aids and films, has been prepared by the National Office. The catalogue and all materials may be obtained through local Heart Associations or the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

MEETINGS CALENDAR

September 9–12: U. S. Section, International College of Surgeons, Chicago, Ill. Karl Meyer, 1516 Lake Shore Drive, Chicago, Ill.

September 29–October 4: College of American Pathologists, New Orleans, La. A. H. Dearing, Prudential Plaza, Suite 2115, Chicago 1, Ill.

October 1–4: American Roentgen Ray Society, Washington, D.C. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa.

October 7–10: American Academy of Pediatrics, Chicago, Ill. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill.

October 14–18: American College of Surgeons, Atlantic City, N. J. Michael L. Mason, 40 E. Erie St., Chicago 11, Ill.

October 14–19: American Society of Anesthesiologists, Los Angeles, Calif. J. E. Remlinger, Jr., 188 W. Randolph St., Chicago 1, Ill.

October 21–23: Association of American Medical Colleges, Atlantic City, N. J. Dean F. Smiley, 2530 Ridge Ave., Evanston, Ill.

October 23–25: American Association of Medical Clinics, Kansas City, Mo. Harold D. Caylor, Caylor-Nickel Clinic, Bluffton, Ind.

October 25–28: Scientific Sessions of the American Heart Association, Chicago, Ill. American Heart Association, 44 East 23rd St., New York 10, N. Y.

November 1–9: School Health Association, Washington, D.C. M. F. Shanholtz, State Office Bldg., Richmond, Va.

November 3–4: American Society for the Study of Arteriosclerosis, Chicago, Ill. O. J. Pollak, M.D., P.O. Box *228, Dover, Del.

November 11–15: American Public Health Association, Cleveland, Ohio. R. M. Atwater, 1790 Broadway, New York 19, N. Y.

November 17–22: Radiological Society of North America, Chicago, Ill. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y.

ABROAD

September 29–October 5: World Medical Association, Istanbul, Turkey. Louis H. Bauer, 10 Columbus Circle, New York 19, N. Y.

October 27–November 2: Congress of International Society of Surgery, Mexico City, Mexico. Dr. L. Dejardin, 141, rue Belliard, Brussels, Belgium.

September 14–21, 1958: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

CONTRIBUTORS TO THIS ISSUE

LUIS M. BECU, M.D.

Fellow in Pathology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

R. I. BIRCHFIELD, M.D.

Fellow in Medicine, Duke Hospital, Durham, N. C.

HERRMAN L. BLUMGART, M.D.

Professor of Medicine, Harvard Medical School; Physician-in-Chief, Beth Israel Hospital, Boston, Mass.

BERNARD L. BROFMAN, M.D.

Director of Cardiovascular Research and Senior Visiting Physician, Mt. Sinai Hospital, Cleveland, Ohio.

G. D. N. BRYANT, M.D.

Assistant Resident in Medicine, Duke Hospital, Durham, N. C.

ALLAN J. DAY, M.B., M.Sc.

Senior Lecturer in Applied Physiology and Pharmacology, University of Adelaide; Clinical Assistant to the Physiology Section, Royal Adelaide Hospital, So. Australia.

JOSEPH EDEIKEN, M.D.

Assistant Professor Clinical Medicine, University of Pennsylvania School of Medicine; Staff Member, Robinette Foundation, Hospital of the University of Pennsylvania; Cardiologist, Southern Division of the Albert Einstein Medical Center, Philadelphia, Pa.

JOHN C. ELDER, M.D.

National Heart Institute Trainee, Mt. Sinai Hospital, Cleveland, Ohio.

A. STONE FREEDBERG, M.D.

Assistant Professor of Medicine, Harvard Medical School; Associate Director of Medical Research, Beth Israel Hospital, Boston, Mass.

HUGH R. GILMORE, M.B., M.R.A.C.P., M.R.C.P.

Senior Lecturer in Medicine, Department of Medicine, University of Adelaide; Assistant Physician, Royal Adelaide Hospital, So. Australia.

SOL GLOTZER, M.D.

Attending Physician, 1st Division, Kings County Hospital Center; Associate Physician, Jewish Chronic Disease Hospital; Chief of Medicine, Williamsburgh General Hospital, Brooklyn, N. Y.

H. GRUSIN, M.B., B.CH., M.R.C.P. (Lond.)

Physician, Baragwanath Hospital and the University of the Witwatersrand, Johannesburg; Presently, at Boksburg-Benoni Hospital, Boksburg, Transvaal, South Africa.

L. L. HEFNER, M.D.

Instructor in Medicine, Department of Medicine, Medical College of Alabama, Birmingham, Ala.; Formerly, Trainee of the National Heart Institute, National Institutes of Health.

W. B. JONES, M.D.

Clinical Investigator, U. S. Veterans Administration Hospital, Birmingham, Ala.; Formerly, Trainee of the National Heart Institute, National Institutes of Health.

THOMAS KILLIP III, M.D.

Research Fellow of the American Heart Association, Department of Medicine, Cornell University Medical College; Physician to Outpatients, New York Hospital, New York, N. Y.

JOHN W. KIRKLIN, M.D., M.S.

Consultant, Section of Surgery, Mayo Clinic; Assistant Professor of Surgery, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

B. J. KOSZEWSKI, M.S., M.D.

Instructor in Medicine, Creighton University School of Medicine, Omaha, Neb.

GEORGE S. KURLAND, M.D.

Associate in Medicine, Harvard Medical School; Assistant Visiting Physician and Associate in Medical Research, Beth Israel Hospital, Boston, Mass.

EUGENE J. LIPPSCHUTZ, M.D.

Director of the Cardiovascular Section, Buffalo General Hospital, Associate Professor of Medicine, University of Buffalo School of Medicine, Buffalo, N. Y.

AGNES LUKAS, M.D.

Resident in Pathology, Buffalo General Hospital, Buffalo, N. Y.

DANIEL S. LUKAS, M.D.

Assistant Professor of Medicine, Cornell University Medical College; Director, Cardio-Pulmonary Laboratory and Assistant Attending Physician, New York Hospital; Assistant Visiting Physician, Second (Cornell) Medical Division, Bellevue Hospital, New York, N. Y.

E. E. MENEFEE, M.D.

Associate Professor of Medicine, Duke Hospital, Durham, N. C.

WILLIAM R. MILNOR, M.D.

Assistant Professor of Medicine, Johns Hopkins University School of Medicine; Physician, Johns Hopkins Hospital, Baltimore, Md.

S. N. MISRA, M.B.B.S.

Registrar in Medicine, Sawai Man Singh Hospital and Medical College, Jaipur, India.

ROBERT A. PEACOCK, M.D.

Assistant Resident in Medicine, Buffalo General Hospital, Buffalo, N. Y.

WILLIAM J. REEDY, M.D., M.Sc.

Assistant Professor of Medicine, Creighton University School of Medicine, Omaha, Neb.

T. J. REEVES, M.D.

Associate Professor, Department of Medicine, Medical College of Alabama, Birmingham, Ala.

L. M. SANGHVI, M.R.C.P. (Lond.) D.T.M. and H. (Eng.)

Reader in Medicine, Sawai Man Singh Hospital and Medical College, Jaipur, India.

COLIN J. SCHWARTZ, M.B.

Junior Medical Research Fellow, National Health and Medical Research Council of Australia; Clinical Assistant to the Physiology Section, Royal Adelaide Hospital, So. Australia.

J. E. SPARKS, M.D.

Medical Arts Building, Huntsville, Ala.; Formerly, Fellow in the Department of Medicine, Medical College of Alabama, Birmingham, Ala.

ISAAC STARR, M.D.

Hartzell Research Professor of Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

H. J. C. SWAN, M.B., M.R.C.P., PH.D.

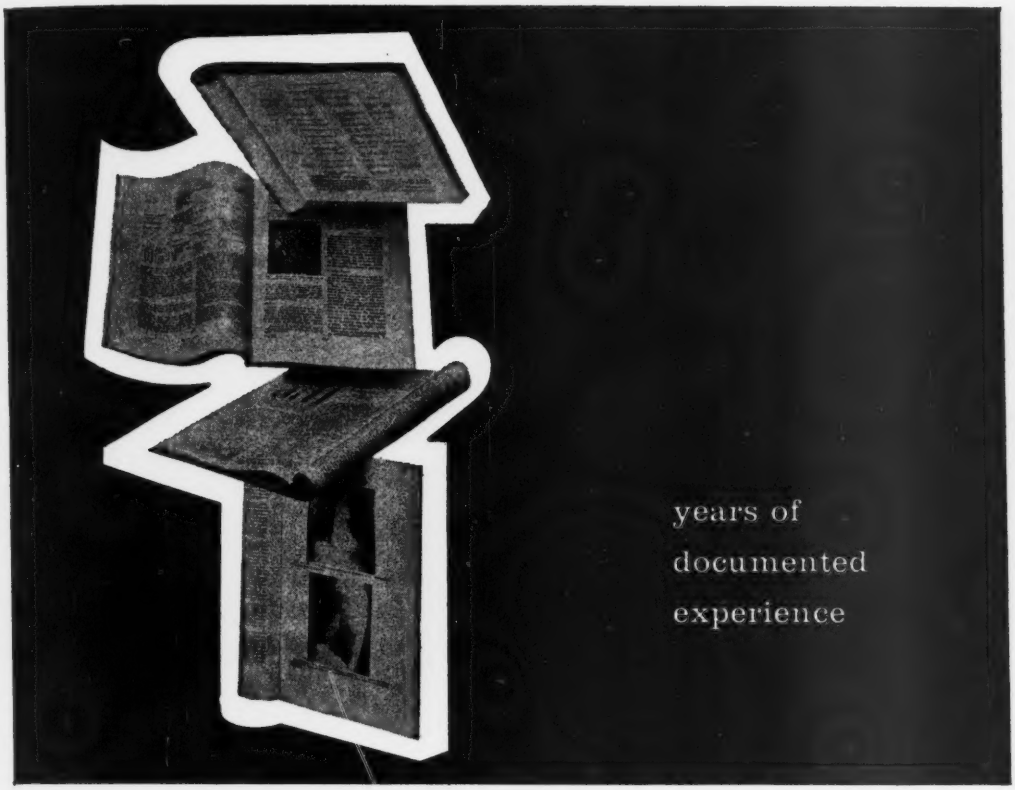
Consultant, Section of Physiology, Mayo Clinic; Assistant Professor of Physiology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

GWENDOLINE K. WILKINSON, M.Sc.

Research Assistant, Department of Human Physiology and Pharmacology, University of Adelaide, So. Australia.

EARL H. WOOD, M.D., PH.D.

Consultant, Section of Physiology, Mayo Clinic; Professor of Physiology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.



YOUR PATIENT NEEDS AN ORGANOMERCURIAL

Practicing physicians know that many years of clinical and laboratory experience with any medication are the only real test of its efficacy and safety.

Among available, effective diuretics, the organomercurials have behind them over three decades of successful clinical use. Their clinical background and thousands of reports in the literature testify to the value of the organomercurial diuretics.

TABLET

NEOHYDRIN®

BRAND OF CHLORMERODRIN (10.3 MG. OF 3-CHLOROMERCURI-2-METHOXY-PROPYLUREA EQUIVALENT TO 10 MG. OF NON-IONIC MERCURY IN EACH TABLET)

a standard for initial control of severe failure

MERCUHYDRIN® SODIUM
BRAND OF MERALLURIDE INJECTION

LAKESIDE

02156

Circulation

JULY 1957
VOL. XVI NO. 1

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

CONTENTS